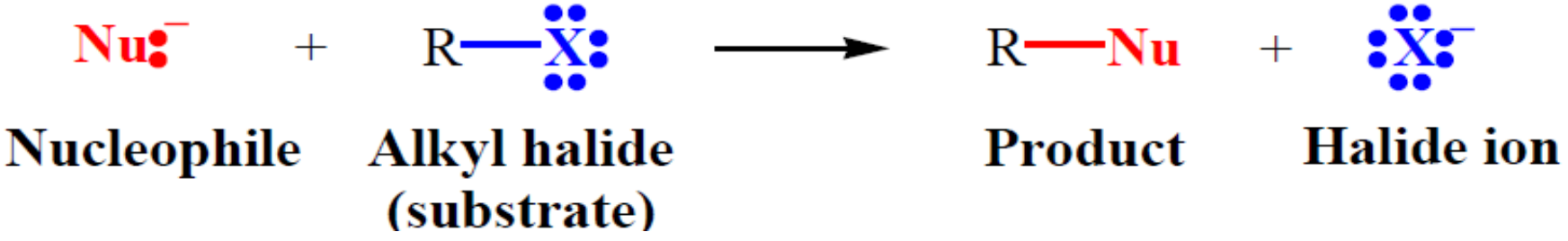
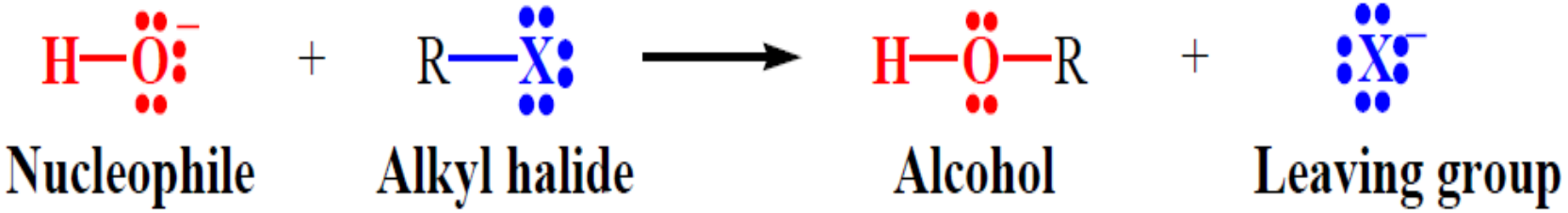
Nucleophilic Substitution Reactions

S_N1 and S_N2



- **A nucleophile, a species with an unshared electron pair (lone-pair electrons), reacts with an alkyl halide (substrate) by replacing the halogen substituent (leaving group).**
- **In nucleophilic substitution reactions, the C–X bond of the substrate undergoes *heterolysis, and the lone-pair electrons of the nucleophile is used to form a new* bond to the carbon atom.**

A **nucleophile is any negative ion or any neutral molecule that has at least one unshared electron pair-*General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion.***



- ***To be a good leaving group the substituent must be able to leave as a relatively stable, weakly basic molecule or ion.***
- **In alkyl halides the leaving group is the halogen substituent — it leaves as a halide ion.**
- **Because halide ions are relatively stable and very weak bases, they are good leaving groups.**

NUCLEOPHILIC SUBSTITUTION REACTION
AN S_N2 REACTION

- **The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion**
- **The reaction is second order overall.**
- **The reaction is first order with respect to methyl chloride and first order with respect to hydroxide ion**

Rate equation: $\text{Rate} \propto [CH_3Cl]\,[OH^-] \Rightarrow \text{Rate} = k\,[CH_3Cl]\,[OH^-]$

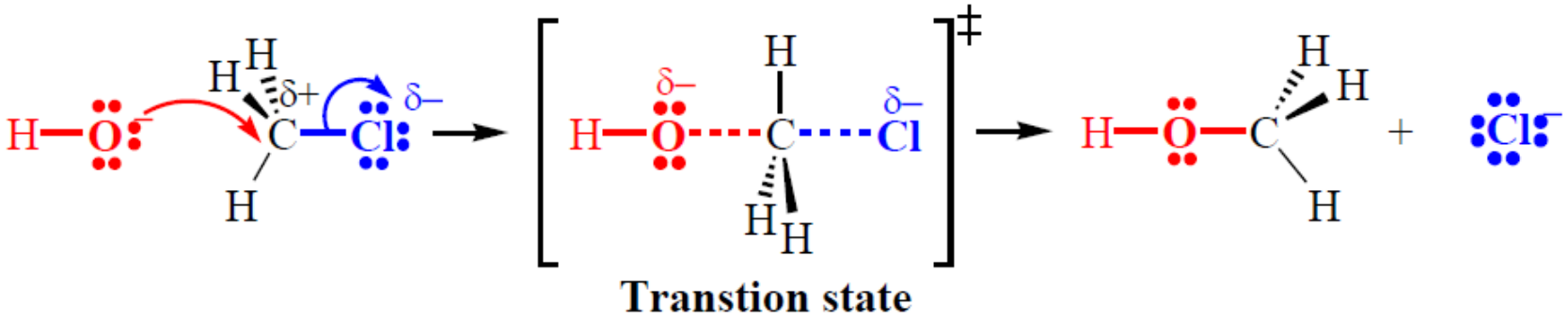
k is the rate constant.

MECHANISM FOR THE S_N2 REACTION

- **The nucleophile attacks the carbon bearing the leaving group from the back side.**
- **The bond between the nucleophile and the carbon atom is forming, and the bond between the carbon atom and the leaving group is breaking.**
- **The configuration of the carbon atom becomes inverted during S_N2 reaction.**
- **Because bond formation and bond breaking occur simultaneously in a single transition state, the S_N2 reaction is a *concerted reaction.***

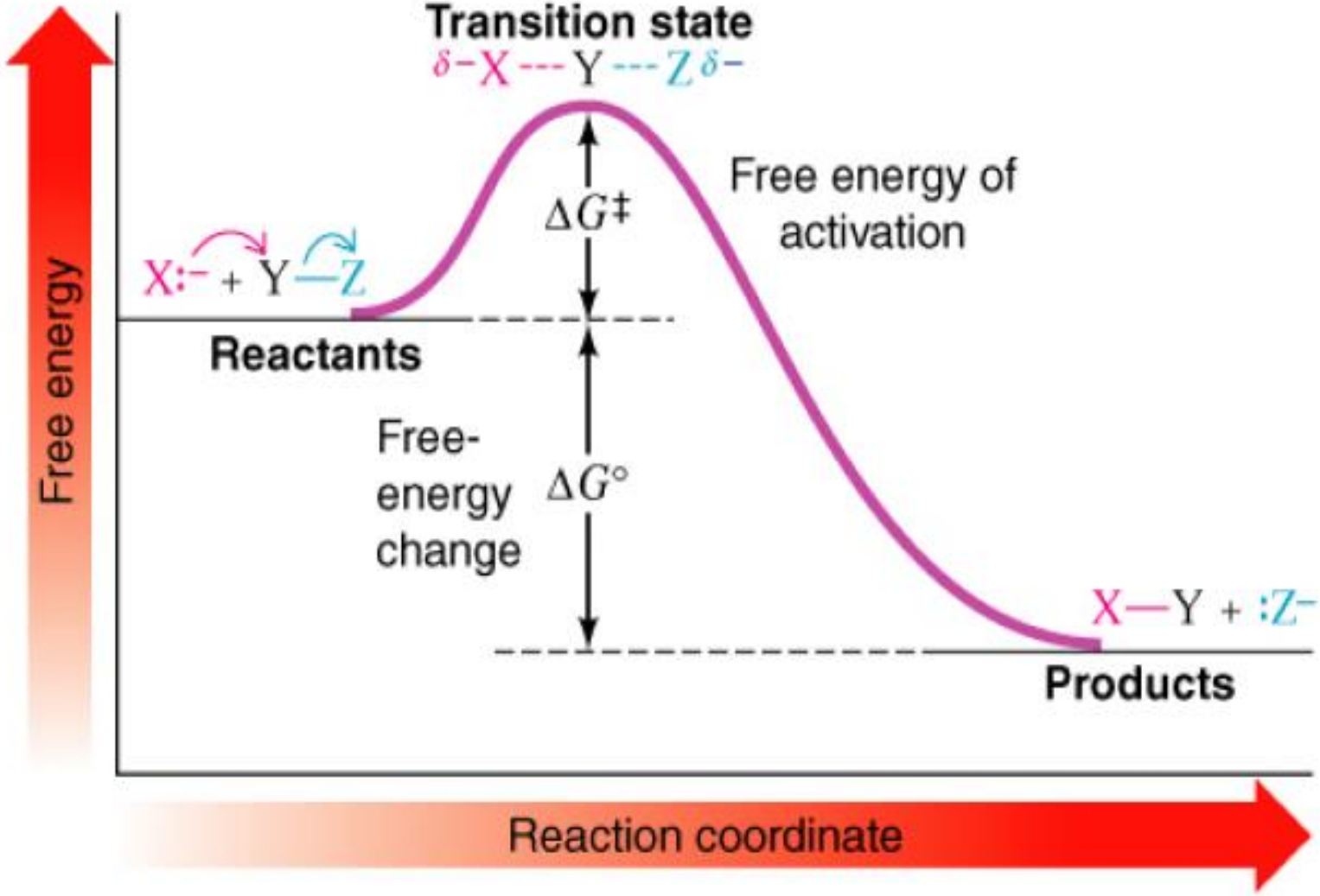
Mechanism

Mechanism:

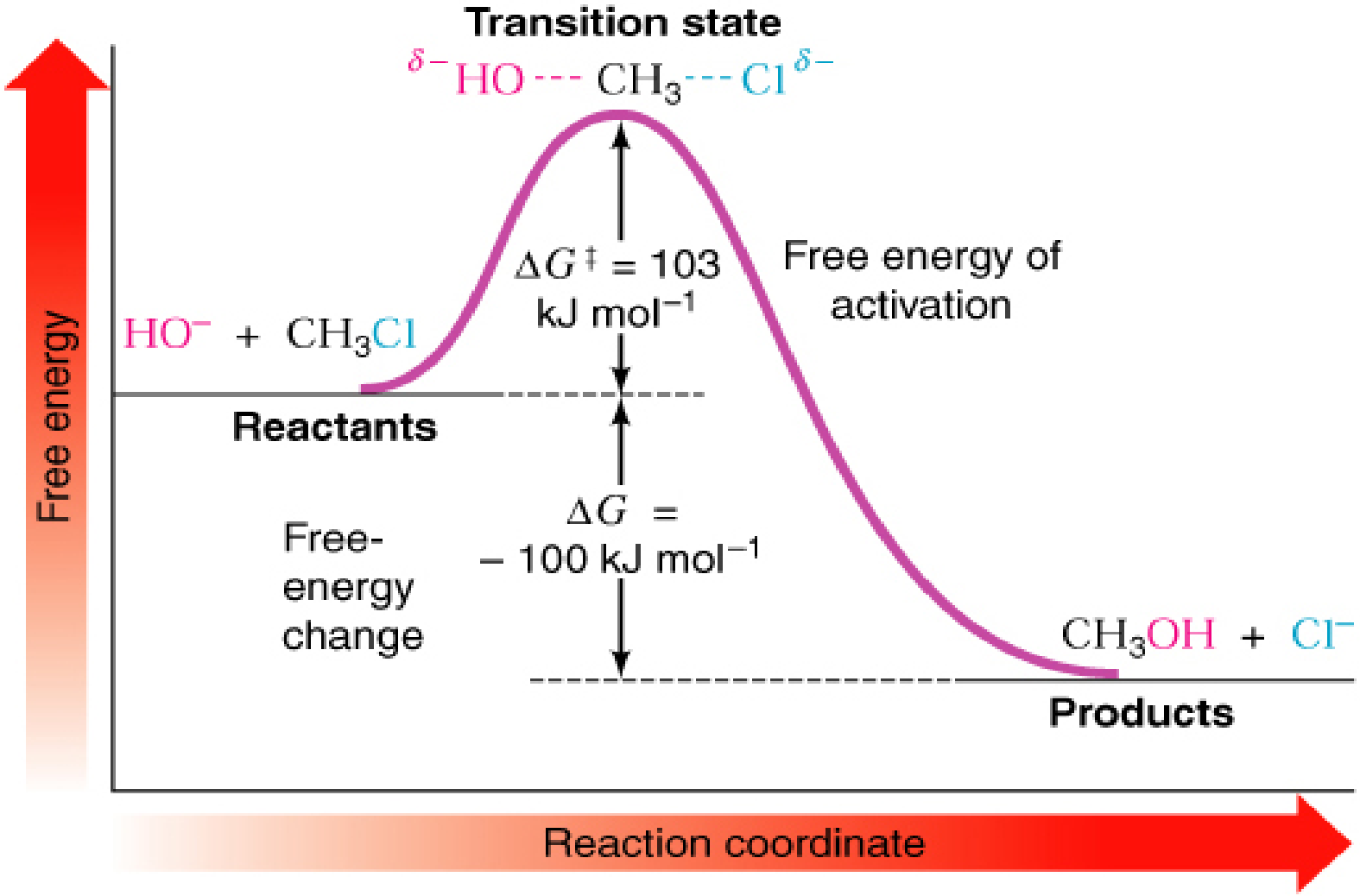


Transtion state

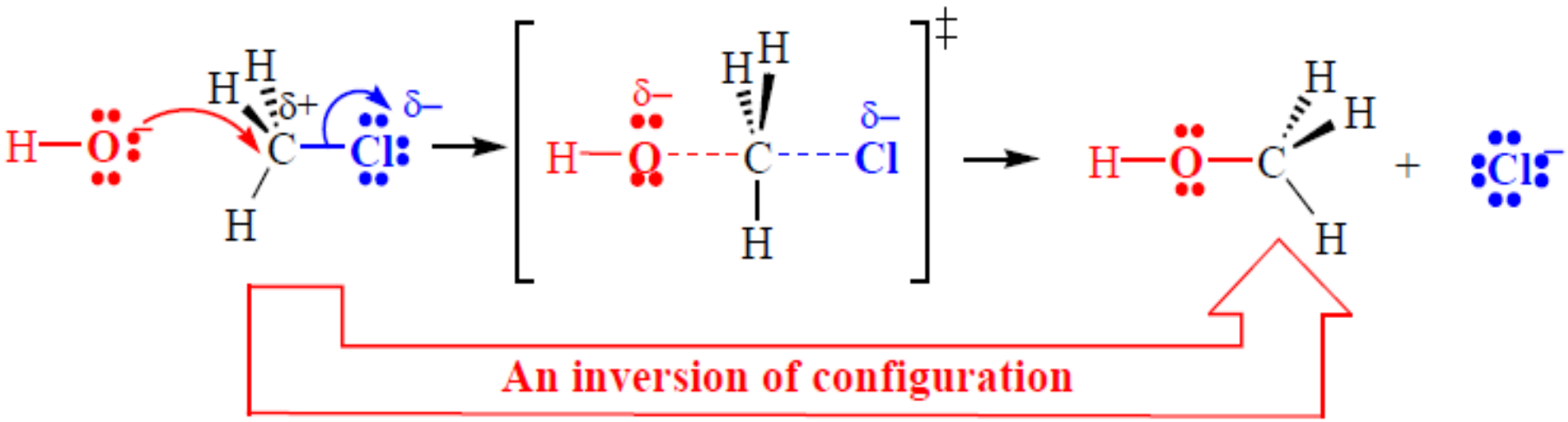
Free Energy Diagram



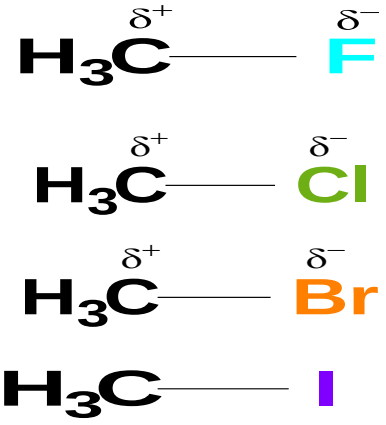
For Methanol



Stereo Chemistry



Reactions of Alkyl Halides (R-X): [SN1, SN2 reactions]



ΔEN (F-C) = (4.0 – 2.5) = 1.5

ΔEN (Cl-C) = (3.0 – 2.5) = 0.5

ΔEN (Br-C) = (2.8 – 2.5) = 0.3

ΔEN (I-C) = (2.5 – 2.5) = 0.0

The α-carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons…

a) the C to X (F, Cl, Br) bond is polar making carbon δ+

b) X (Cl, Br, I) is a leaving group

decreasing basicity, increasing stability

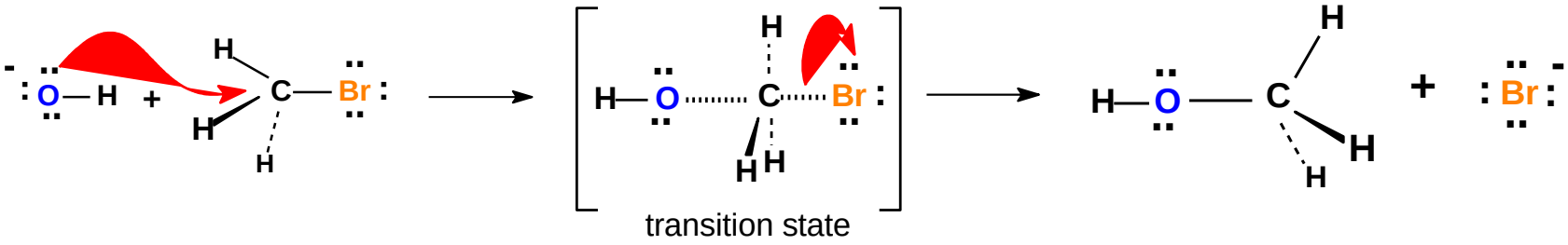
The best leaving groups are the weakest bases.

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7
I^-	Br^-	Cl^-	F^-	HO^-
30,000	10,000	200	1	0

The poorest leaving groups are the strongest bases.

increasing leaving ability

2nd Order Nucleophilic Substitution Reactions, i.e., S_N2 reactions



The rate of an S_N2 reaction depends upon 4 factors:

1. The nature of the substrate (the alkyl halide)
2. The power of the nucleophile
3. The ability of the leaving group to leave
4. The nature of the solvent

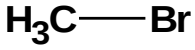
1. Consider the nature of the substrate:

- Unhindered alkyl halides, those in which the back side of the α-carbon is not blocked, will react fastest in S_N2 reactions, that is:

  Me° >> 1° >> 2° >> 3°

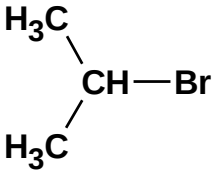
- While a methyl halides reacts quickly in S_N2 reactions, a 3° does not react. The back side of an α-carbon in a 3° alkyl halide is completely blocked.

Effect of nature of substrate on rate of S_N2 reactions:

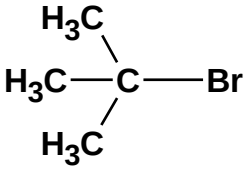


methyl bromide

ethyl bromide

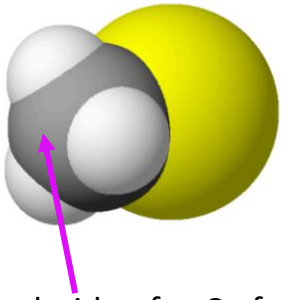


isopropyl bromide

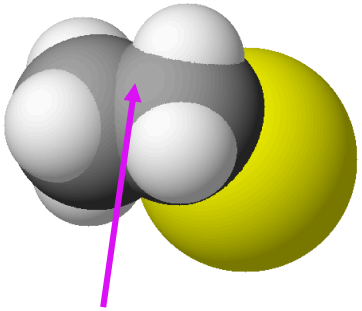


t-butyl bromide

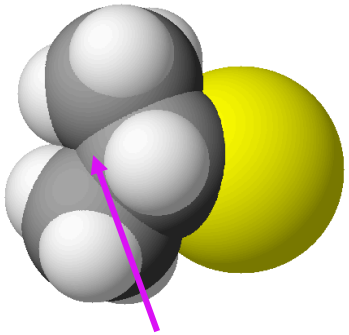
SPACE FILLING MODELS SHOW ACTUAL SHAPES AND RELATIVE SIZES



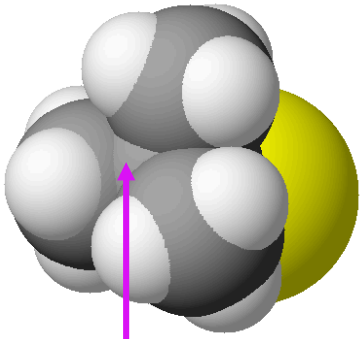
Back side of α-C of a methyl halide is unhindered.



Back side of α-C of a 1° alkyl halide is slightly hindered.



Back side of α-C of a 2° alkyl halide is mostly hindered.



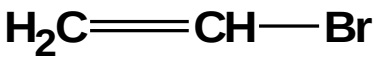
Back side of α-C of a 3° alkyl halide is completely blocked.

- **Me° >> 1° >> 2° >> 3°**

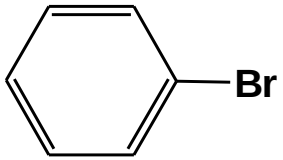
decreasing rate of *S_N2 reactions*

Effect of the nucleophile on rate of S_N2 reactions:

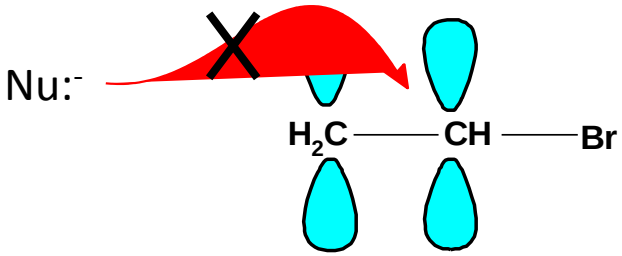
- **The α-carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions.**

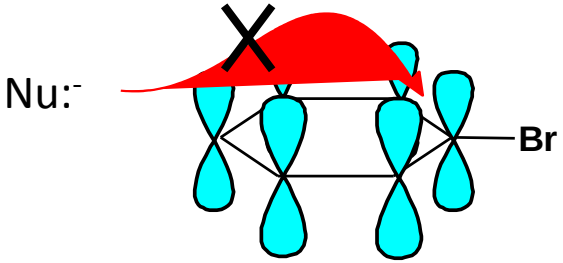


vinyl bromide



bromobenzene





The overlapping p-orbitals that form the π-bonds in vinyl and aryl halides completely block the access of a nucleophile to the back side of the α-carbon.

Effect of nature substrate on rate of S_N2 reactions:

Consider the power of the nucleophile:

- **The better the nucleophile, the faster the rate of S_N2 reactions.**
- **The table below show the relative power or various nucleophiles.**
- **The best nucleophiles are the best electron donors.**

Reactivity	Nu:$^-$	Relative Reactivity
very weak	HSO_4^-, $H_2PO_4^-$, RCOOH	< 0.01
weak	ROH	1
	HOH, NO_3^-	100
fair	F^-	500
	Cl^-, $RCOO^-$	20×10^3
	NH_3, CH_3SCH_3	300×10^3
good	N_3^-, Br^-	600×10^3
	OH^-, CH_3O^-	2×10^6
very good	CN^-, HS^-, RS^-, $(CH_3)_3P$:, NH_2^- ,RMgX, I^-, H^-	$> 100 \times 10^6$

Effect of nature of the leaving group on rate of S_N2 reactions:

- **3. Consider the nature of the leaving group:**

- **The leaving group usually has a negative charge**
- ❑ **Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.**
- ❑ **Weak bases are readily identified. They have high pKb values.**

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7	pKb = -2	pKb = -21
I^-	Br^-	Cl^-	F^-	HO^-	RO^-	H_2N^-
30,000	10,000	200	1	0	0	0

Increasing leaving ability

- ❑ **Iodine (-I) is a good leaving group because iodide (I^-) is non basic.**
- ❑ **The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH^-) is a strong base.**

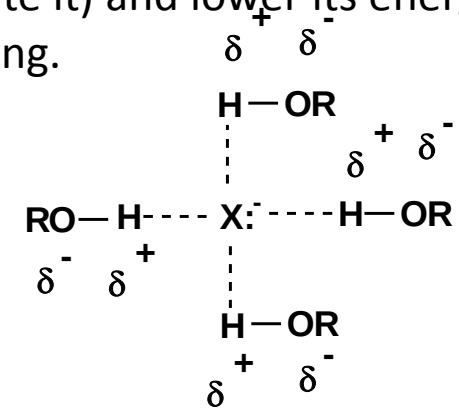
Effect of the solvent on rate of S_N2 reactions:

- **4. Consider the nature of the solvent:**

- **There are 3 classes of organic solvents:**

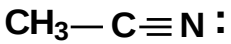
- ❑ **Protic solvents, which contain –OH or –NH_2 groups. Protic solvents slow down S_N2 reactions.**
- ❑ **Polar aprotic solvents like acetone, which contain strong dipoles but no –OH or –NH_2 groups. Polar aprotic solvents speed up S_N2 reactions.**
- ❑ **Non polar solvents, e.g., hydrocarbons. S_N2 reactions are relatively slow in non polar solvents.**

Protic solvents (e.g., H_2O, MeOH, EtOH, CH_3COOH, etc.) cluster around the Nu:- (solvate it) and lower its energy (stabilize it) and reduce its reactivity via H-bonding.



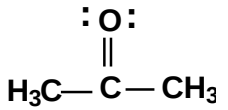
A solvated anion (Nu:-) has reduced nucleophilicity, reduced reactivity and increased stability

A solvated nucleophile has difficulty hitting the α-carbon.



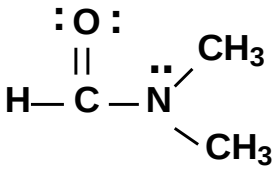
acetonitrile

Effect of the solvent on rate of S_N2 reactions:

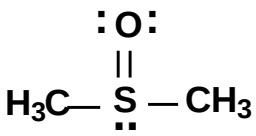


acetone

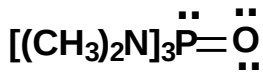
- Polar Aprotic Solvents solvate the cation counterion of the nucleophile but not the nucleophile.
- Examples include acetonitrile (CH_3CN), acetone (CH_3COCH_3), dimethylformamide (DMF) [$(CH_3)_2NC{=}OH$], dimethyl sulfoxide, DMSO [$(CH_3)_2SO$], hexamethylphosphoramide, HMPA {$[(CH_3)_2N]_3PO$} and dimethylacetamide (DMA).



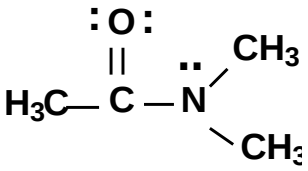
DMF



DMSO

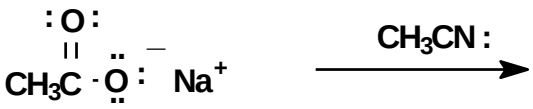


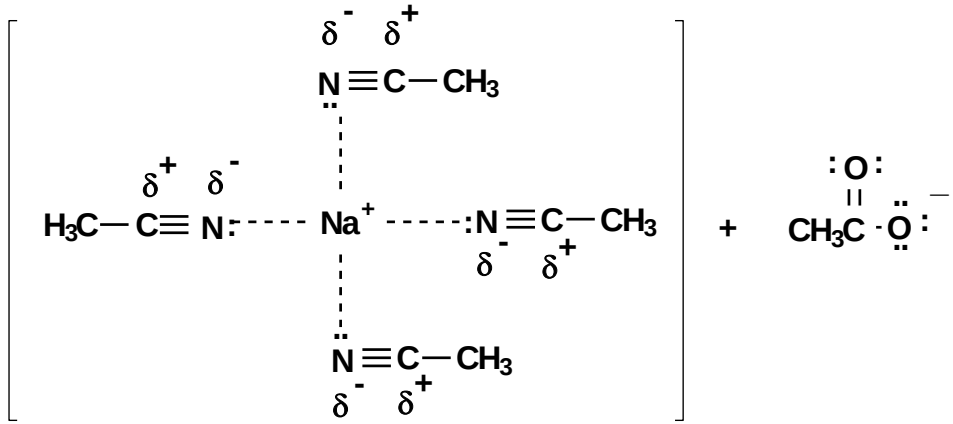
HMPA



DMA

Polar aprotic solvents solvate metal cations leaving the anion counterion (Nu: $^-$) bare and thus more reactive



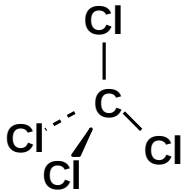


Effect of the solvent on rate of S_N2 reactions:

•Non polar solvents (benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles.

– **S_N2 reactions are relatively slow in non polar solvents similar to that in protic solvents.**

benzene

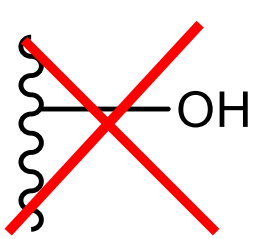


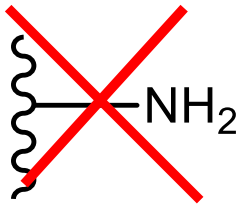
carbon tetrachloride

n-hexane

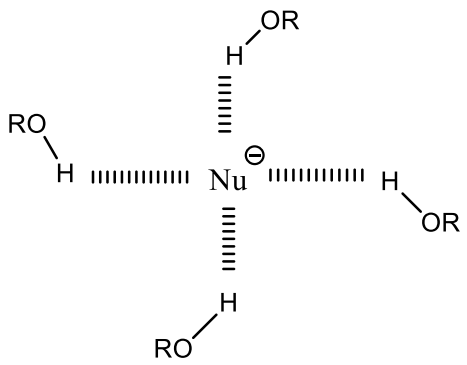
Solvent Effect for S_N2 reactions

- Requires a polar, aprotic solvent…
- NO alcohols or amines



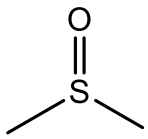


Why…because hydrogen bonding with the nucleophile can occur…slowing down the reaction



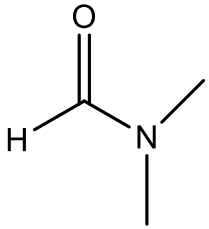
Polar, Aprotic Solvents

DMSO

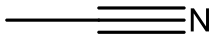


dimethyl sulfoxide

DMF

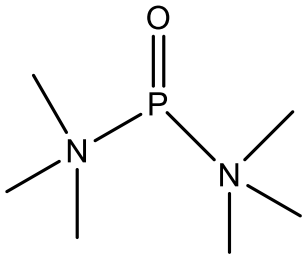


dimethyl formamide



acetonitrile

HMPA



hexamethyl phosphamide

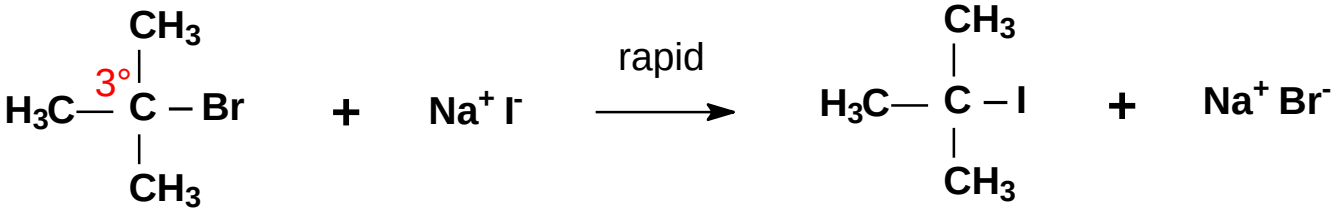
S_N2 Conditions Summary

- 1) Substrate (methyl > primary > secondary >> tertiary)
- 2) Nucleophile (negative charge > neutral)
- 3) leaving group (Y) (Y stabilizes a negative charge)
- 4) solvent (needs to be polar and aprotic)

AN S_N1 REACTION

- **THE REACTION OF *TERT-BUTYL CHLORIDE WITH* HYDROXIDE ION**

1st Order Nucleophilic Substitution Reactions, i.e., S_N1 reactions



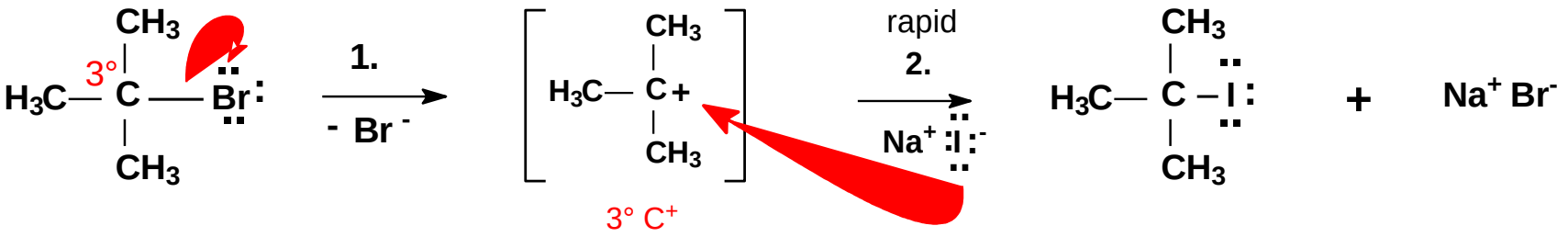
- **3° alkyl halides are essentially inert to substitution by the S_N2 mechanism because of steric hindrance at the back side of the a-carbon.**
- **Despite this, 3° alkyl halides do undergo nucleophilic substitution reactions quite rapidly , but by a different mechanism, i.e., the S_N1 mechanism.**
- **S_N1 = Substitution, Nucleophilic, 1st order (unimolecular).**
- **S_N1 reactions obey 1st order kinetics, i.e., Rate = k·[RX].**
- **The rate depends upon the concentration of only 1 reactant, the alkyl halide-not the nucleophile**
- **The order of reactivity of substrates for S_N1 reactions is the reverse of S_N2**

- **3° > 2° > 1° > vinyl > phenyl > Me°**
- **R_3C-Br R_2HC-Br RH_2C-Br CH_2=CH-Br ϕ-Br H_3C-Br**

increasing rate of S_N1 reactions

Mechanism of S_N1 reactions

- **The mechanism of an S_N1 reaction occurs in 2 steps:**



- **Reaction Steps …**

1. **the slower, rate-limiting dissociation of the alkyl halide forming a C+ intermediate**
2. **a rapid nucleophilic attack on the C+**

Note that the nucleophile is not involved in the slower, rate-limiting step.

The Rate of S_N1 reactions

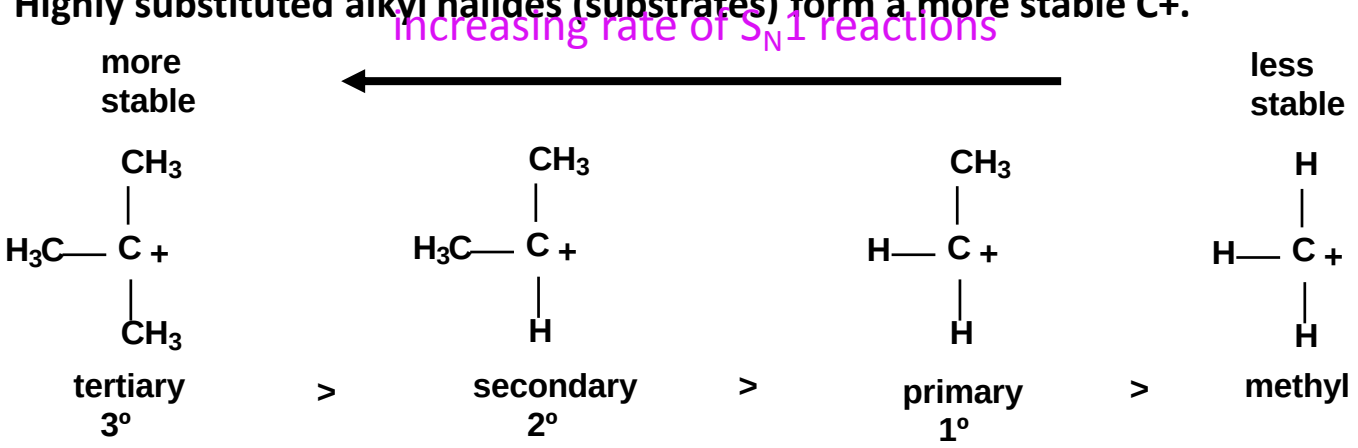
- **The rate of an S_N1 reaction depends upon 3 factors:**

1. **The nature of the substrate (the alkyl halide)**
2. **The ability of the leaving group to leave**
3. **The nature of the solvent**

- **The rate is independent of the power of the nucleophile.**

• 1. Consider the nature of the substrate:

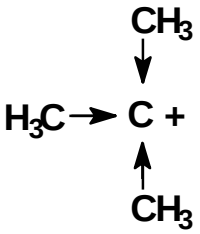
Highly substituted alkyl halides (substrates) form a more stable C+.



Stability of Carbocations

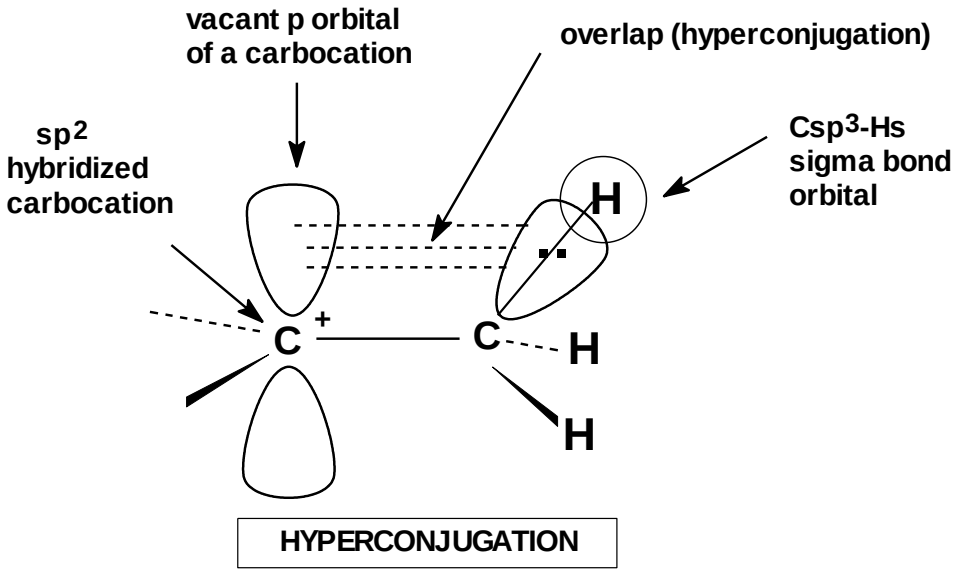
- **Alkyl groups are weak electron donors.**

❑ **They stabilize carbocations by donating electron density by induction (through σ bonds)**



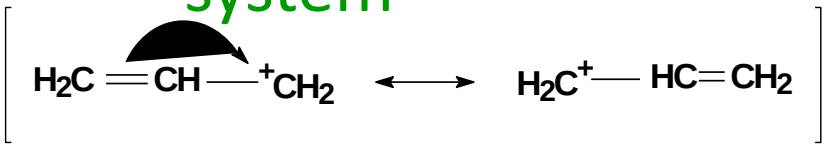
Inductive effects:
Alkyl groups donate (shift) electron density through sigma bonds to electron deficient atoms.
This stabilizes the carbocation.

❑ **They stabilize carbocations by hyperconjugation (by partial overlap of the alkyl C-to-H bonds with the empty p-orbital of the carbocation).**

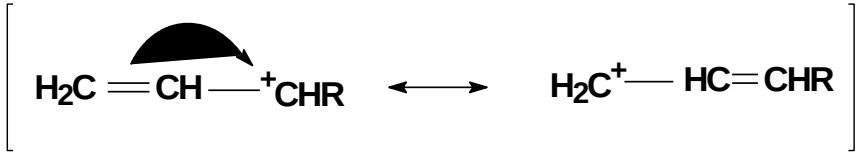


Stability of Carbocations

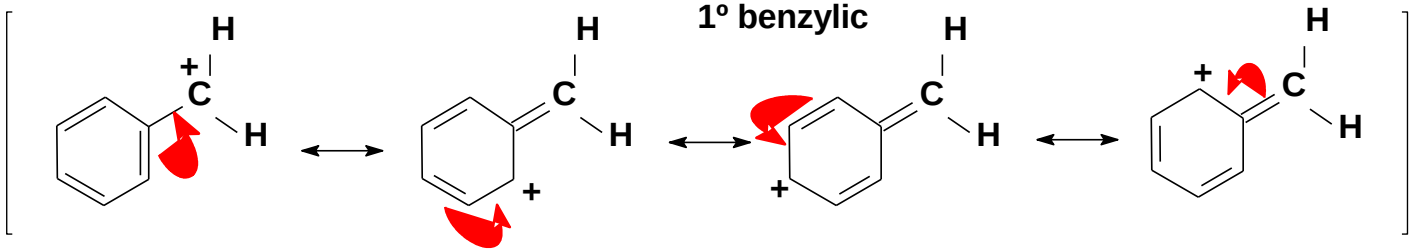
- Allyl and benzyl halides also react quickly by S_N1 reactions because their carbocations are unusually stable due to their resonance forms which delocalize charge over an extended π system



1° allyl carbocation

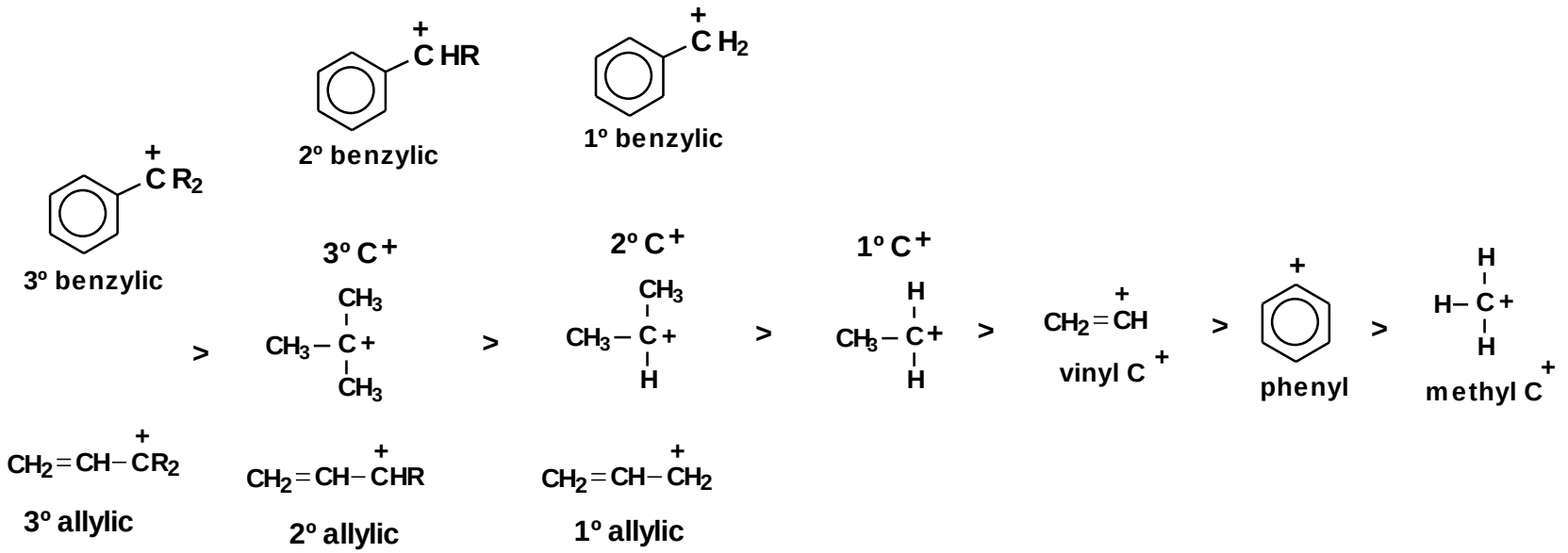


2° allyl carbocation



Relative Stability of All Types of Carbocations

Increasing C+ stability and rate of S_N1 reaction



Note that 1° allylic and 1° benzylic C+'s are about as stable as 2°alkyl C+'s.

Note that 2° allylic and 2° benzylic C+'s are about as stable as 3° alkyl C+'s.

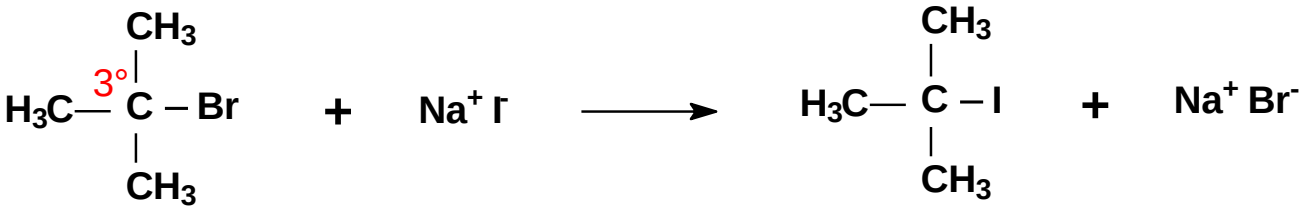
Note that 3° allylic and 3° benzlic C+'s are more stable than 3° alkyl C+'s

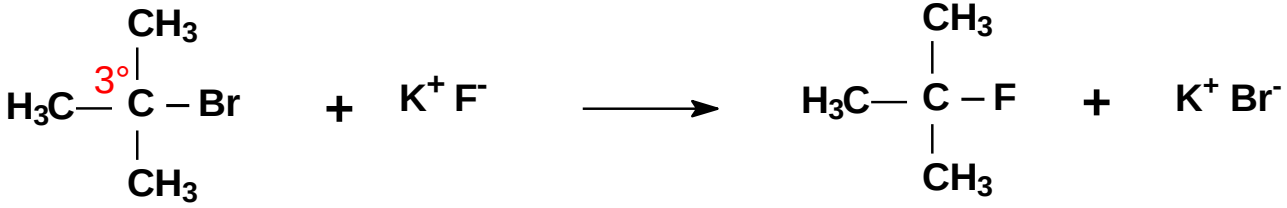
Note that phenyl and vinyl C+'s are unstable. Phenyl and vinyl halides do not usually react by S_N1 or S_N2 reactions

Effect of the nucleophile on rate of S_N1 reactions:

- **Consider the nature of the Nucleophile:**

- **Recall again that the nature of the nucleophile has no effect on the rate of S_N1 reactions because the slowest (rate-determining) step of an S_N1 reaction is the dissociation of the leaving group and formation of the carbocation.**
- **All carbocations are very good electrophiles (electron acceptors) and even weak nucleophiles, like H_2O and methanol, will react quickly with them.**
- **The two S_N1 reactions will proceed at essentially the same rate since the only difference is the nucleophile.**





Effect of nature of the leaving group on rate of S_N1 reactions:

- 2. **Consider the nature of the leaving group:**
- **The nature of the leaving group has the same effect on both S_N1 and S_N2 reactions.**
- **The better the leaving group, the faster a C+ can form and hence the faster will be the S_N1 reaction.**
- **The leaving group usually has a negative charge**

❑ **Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.**

❑ **Weak bases are readily identified. They have high pKb values.**

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7	pKb = -2	pKb = -21
I^-	Br^-	Cl^-	F^-	HO^-	RO^-	H_2N^-
30,000	10,000	200	1	0	0	0

Increasing leaving ability

❑ Iodine (-I) is a good leaving group because iodide (I^-) is non basic.

❑ The hydroxyl group (-OH) is a poor leaving group because hydroxide (OH^-) is a strong base.

Effect of the solvent on rate of S_N1 reactions:

- 3. **Consider the nature of the solvent:**

- **For S_N1 reactions, the solvent affects the rate only if it influences the stability of the charged transition state, i.e., the C+. The Nu:$^-$ is not involved in the rate determining step so solvent effects on the Nu:$^-$ do not affect the rate of S_N1 reactions.**
- **Polar solvents, both protic and aprotic, will solvate and stabilize the charged transition state (C+ intermediate), lowering the activation energy and accelerating S_N1 reactions.**
- **Nonpolar solvents do not lower the activation energy and thus make S_N1 reactions relatively slower**

The relative rates of an S_N1 reaction due to solvent effects are given

$$(CH_3)_3C\text{-}Cl + ROH \rightarrow (CH_3)_3C\text{-}OR + HCl$$

H_2O	20% EtOH (aq)	40% EtOH (aq)	EtOH
100,000	14,000	100	1

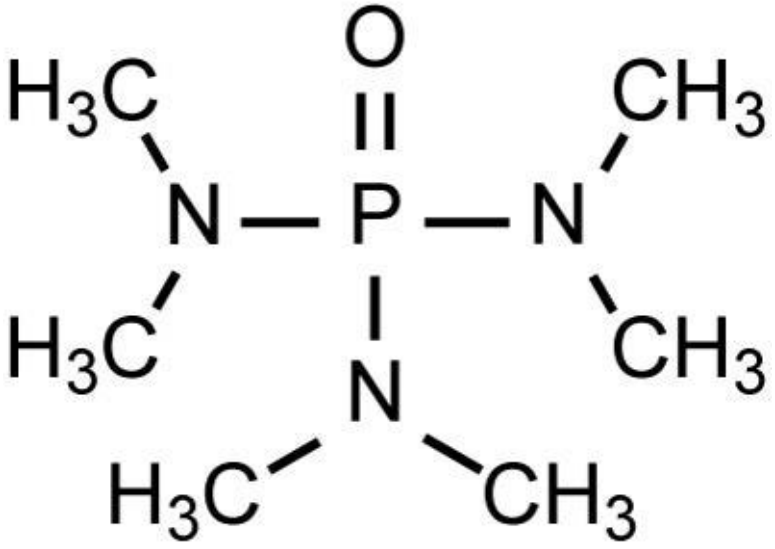
reaction rate increases with polarity of solvent

Effect of the solvent on rate of S_N1 reactions:

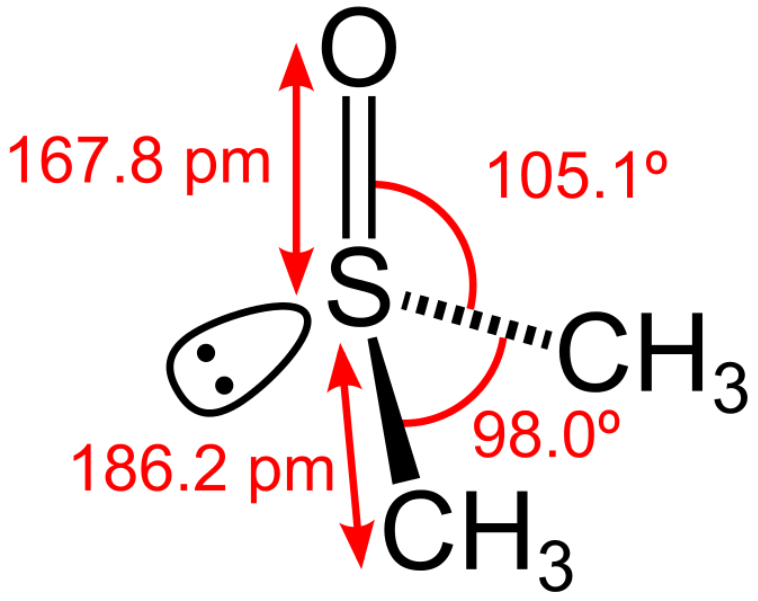
- **Solvent polarity is usually expressed by the "dielectric constant", ε, which is a measure of the ability of a solvent to act as an electric insulator.**
- **Polar solvents are good electric insulators because their dipoles surround and associate with charged species.**
- **Dielectric constants of some common solvents are given in the following table**

name	dielectric constant	name	dielectric constant
aprotic solvents		**protic solvents**	
hexane	**1.9**	acetic acid	6.2
benzene	2.3	acetone	20.7
diethyl ether	4.3	ethanol	24.3
chloroform	4.8	methanol	33.6
HMPA	30	formic acid	58.0
DMF	38	**water**	**80.4**
DMSO	48		

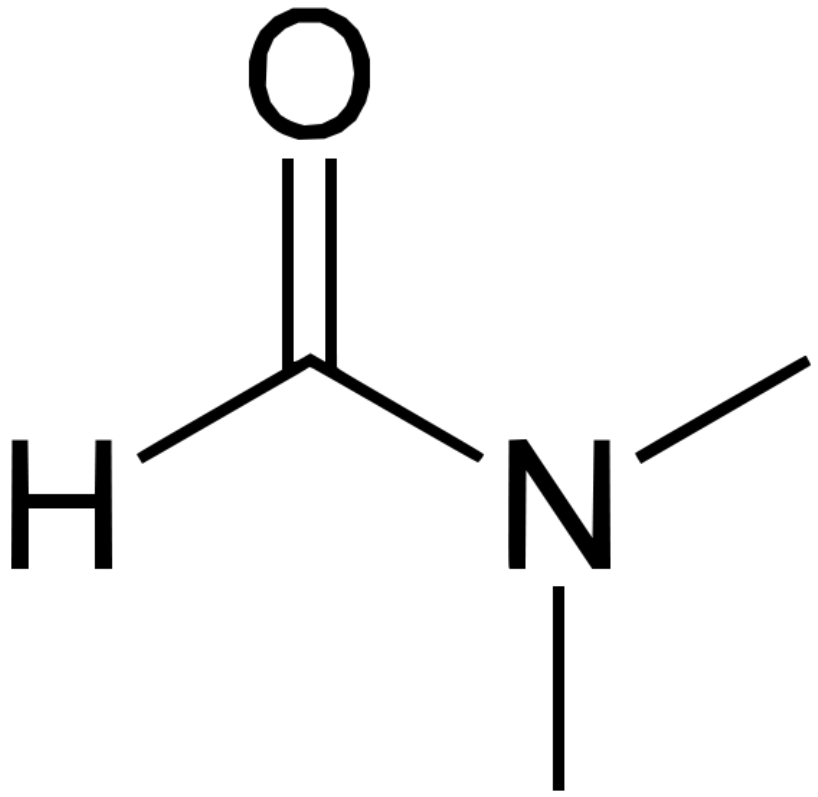
HMPA


O
H3C
CH3
N
P
N
H3C
CH3
N
H3C
CH3

DMSO


O
167.8 pm
105.1°
S
CH3
98.0°
186.2 pm
CH3

DMF



Reactivity of alkyl halides toward substitution and elimination

Halide type	*S_N1*	*S_N2*	*E1*	*E2*
Primary halide	Does not occur	**Highly favored**	Does not occur	Occurs when strong, hindered bases are used
Secondary halide	Can occur under solvolysis conditions in polar solvents	**Favored by good nucleophiles in polar aprotic solvents**	Can occur under solvolysis conditions in polar solvents	**Favored when strong bases are used**
Tertiary halide	**Favored by nonbasic nucleophiles in polar solvents**	Does not occur	Occurs under solvolysis conditions	**Highly favored when bases are used**

Effects of reaction variables on substitution and elimination reactions

Reaction	*Solvent*	*Nucleophile/base*	Leaving group	Substrate structure
S_N1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by good nucleophile/weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
S_N2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by good nucleophile/ weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 1°, allylic, and benzylic substrates
E1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
E2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by poor nucleophile/ strong base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3° substrates

Overall Summary of S_N1, S_N2, E1 and E2 Reactions

CH_3X	RCH_2X	RR'CHX	RR'R"CX
Methyl	**1°**	**2°**	**3°**
	Bimolecular reactions	**only**	**S_N1/E1 or E2**
Gives S_N2 reactions	Gives mainly S_N2 except with a hindered strong base [e.g., $(CH_3)_3CO^-$] and then gives mainly E2	Gives mainly S_N2 with weak bases (e.g., I^-, CN^-, RCO_2^-) and mainly E2 with strong bases (e.g., RO^-)	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used E2 predominates

Neighboring Group Participation

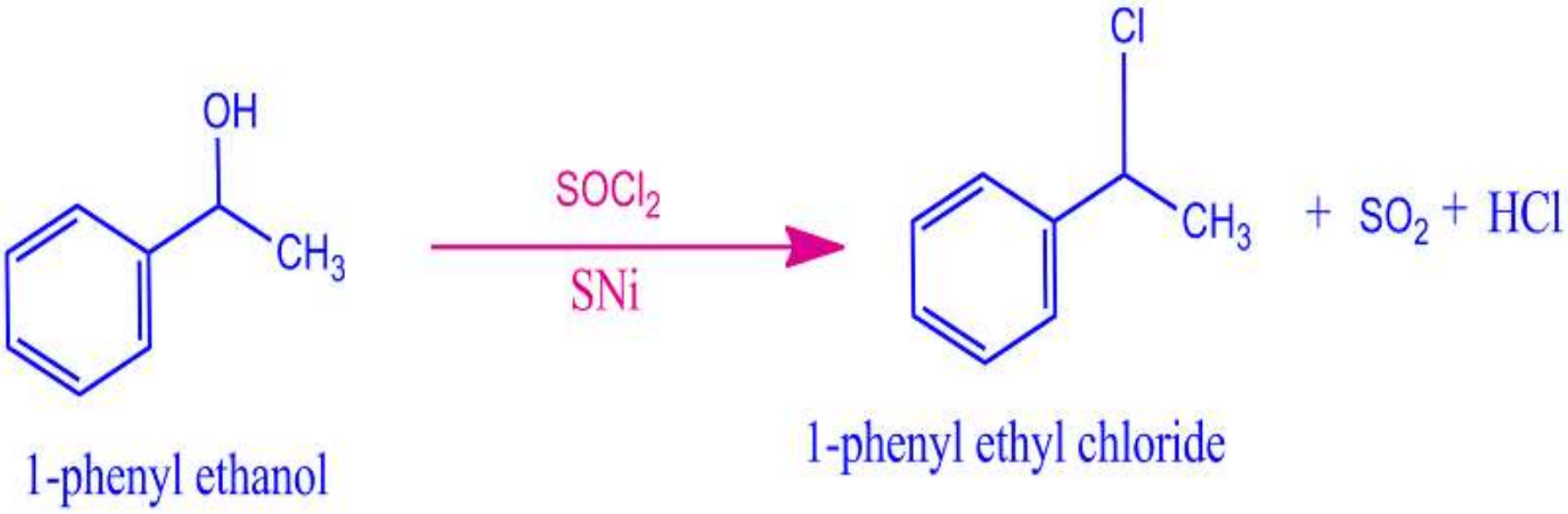
nucleophilic substitution can also be an intramolecular process. In an intramolecular reaction, called neighboring group participation,the presence of functional groups in the substrate other than the leaving group affects the rate and/or the stereochemistry of the reaction. Thus, when the nucleophile and leaving groups are a part of the same molecule, the result is a cyclic compound.

SNi Reaction

- The term SNi stands for substitution nucleophilic internal. In SN1 and SN2 **reaction** mechanism, the **racemization and inversion of the configuration** of the product take place.

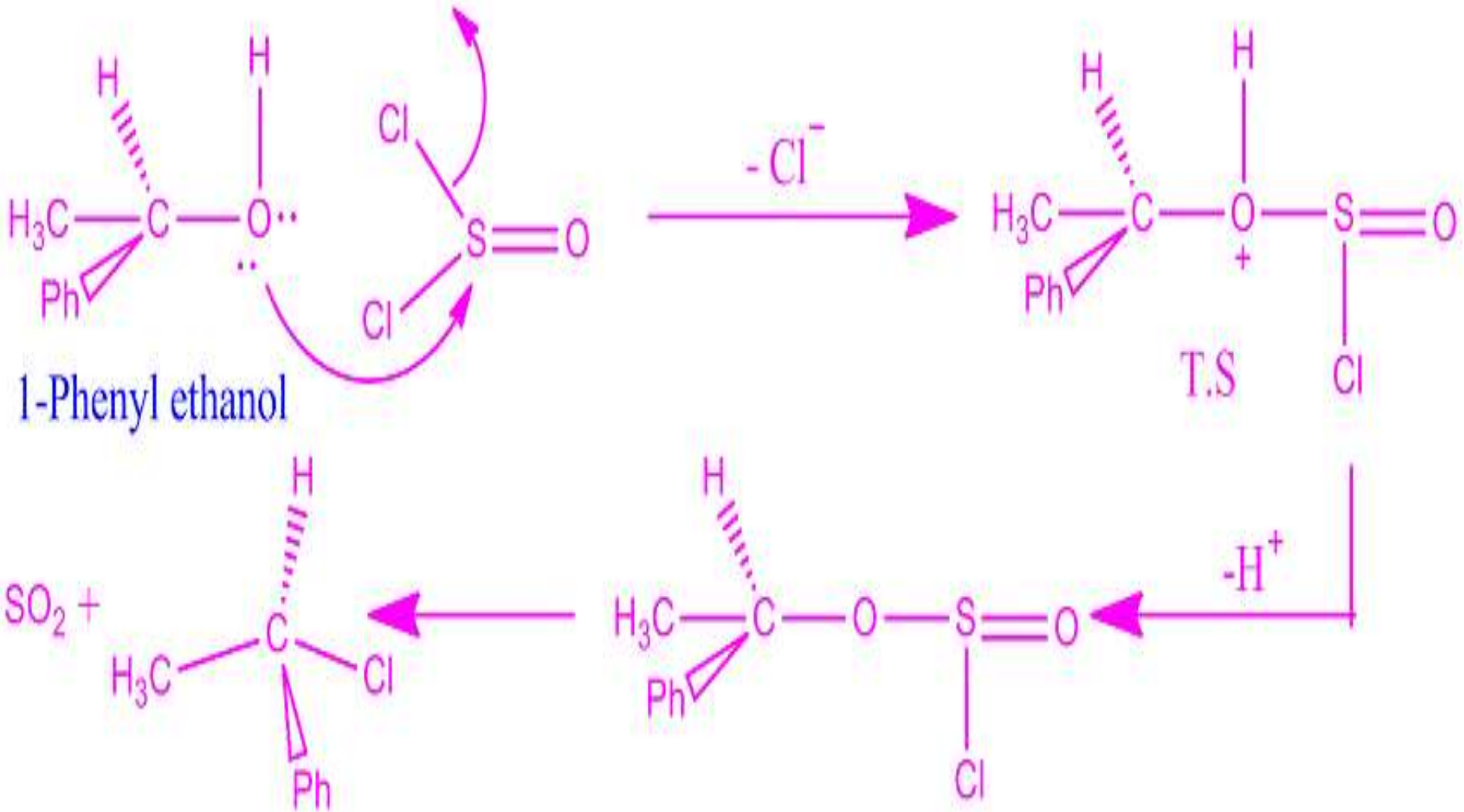
- But Hughes, Ingold has shown that optically active **1-phenyl ethanol** reacts with thionyl chloride to give 1-phenyl ethyl chloride with complete retention of configuration.

  Normally the product should be inversion of configuration. so former can be explained by internal mechanism which is **called SNi mechanism.**



1-phenyl ethanol

1-phenyl ethyl chloride

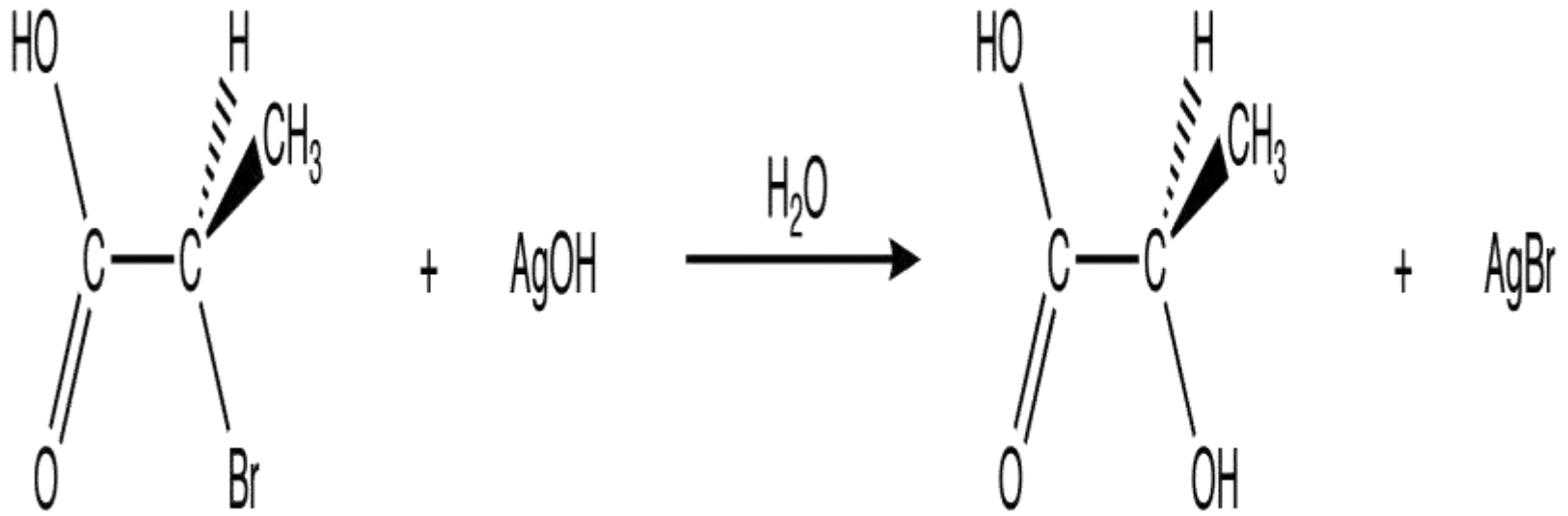

H
H
H3C
C
O
Ph
Cl
S
O
Cl
- Cl⁻
T.S
+
-H⁺
SO2 +
1-Phenyl ethanol
1-Phenyl ethyl chloride

Stereo chemistry of SNi reaction

- During the **SNi reaction** there occurs a internal transformation through a cyclic transition state to which attack of chloride from front side leads to **retention in configuration.**
- That is, both the **reactant and products are having same configuration.**

Neighboring Group Participation

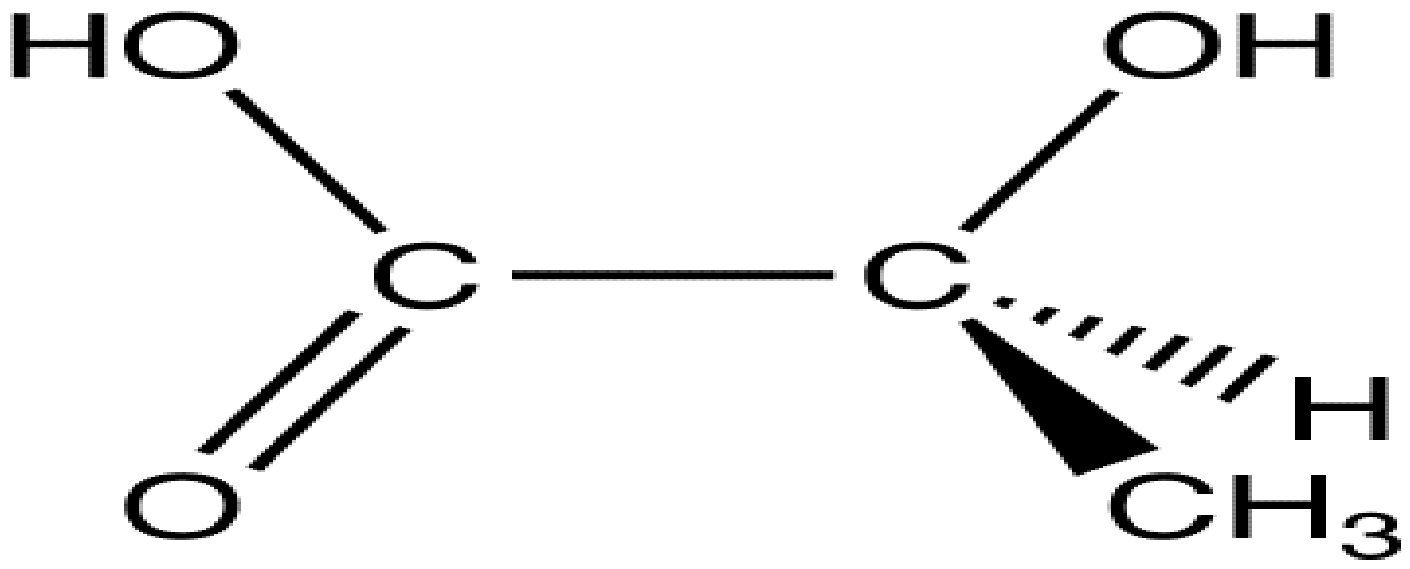
- Some nucleophilic aliphatic substitution reactions that are overall *intermolecular* evidently begin with a nucleophilic atom in the substrate reacting *intramolecularly* with the carbon atom bearing the leaving group expelling the leaving group. The resultant intermediate then reacts with the external nucleophile giving the observed substitution product, which is an intermolecular nucleophilic substitution. The role of the nucleophilic atom in the substrate in the overall reaction is known as neighboring group participation or anchimeric assistance.



1

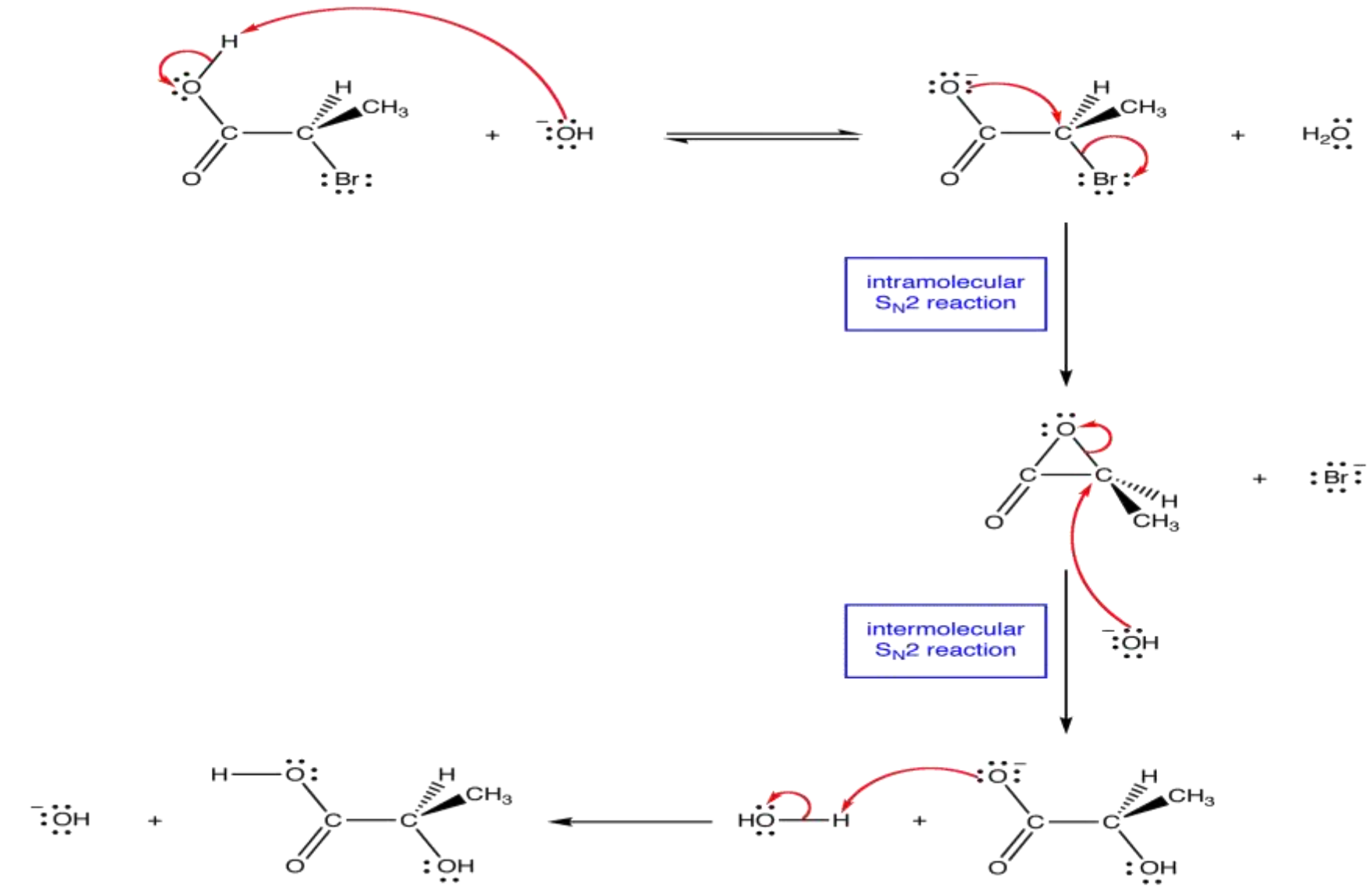
2

- The net reaction is a nucleophilic substitution in which **1** is the substrate and **2** the substitution product. If the reaction were to proceed via S_N1 mechanism, it would yield, as substitution products, **2**, with retention of configuration at the chiral center, and its enantiomer **(3)**, with inversion of configuration.



3

- If the reaction were to proceed via S_N2 mechanism, it would occur with inversion of configuration at the chiral center, yielding **3** as the only substitution product. The formation of **2** as the only substitution product indicates that the reaction is not a simple intermolecular nucleophilic aliphatic substitution that follows either S_N1 or S_N2 path. Neighboring group participation is invoked to explain the course of the reaction.

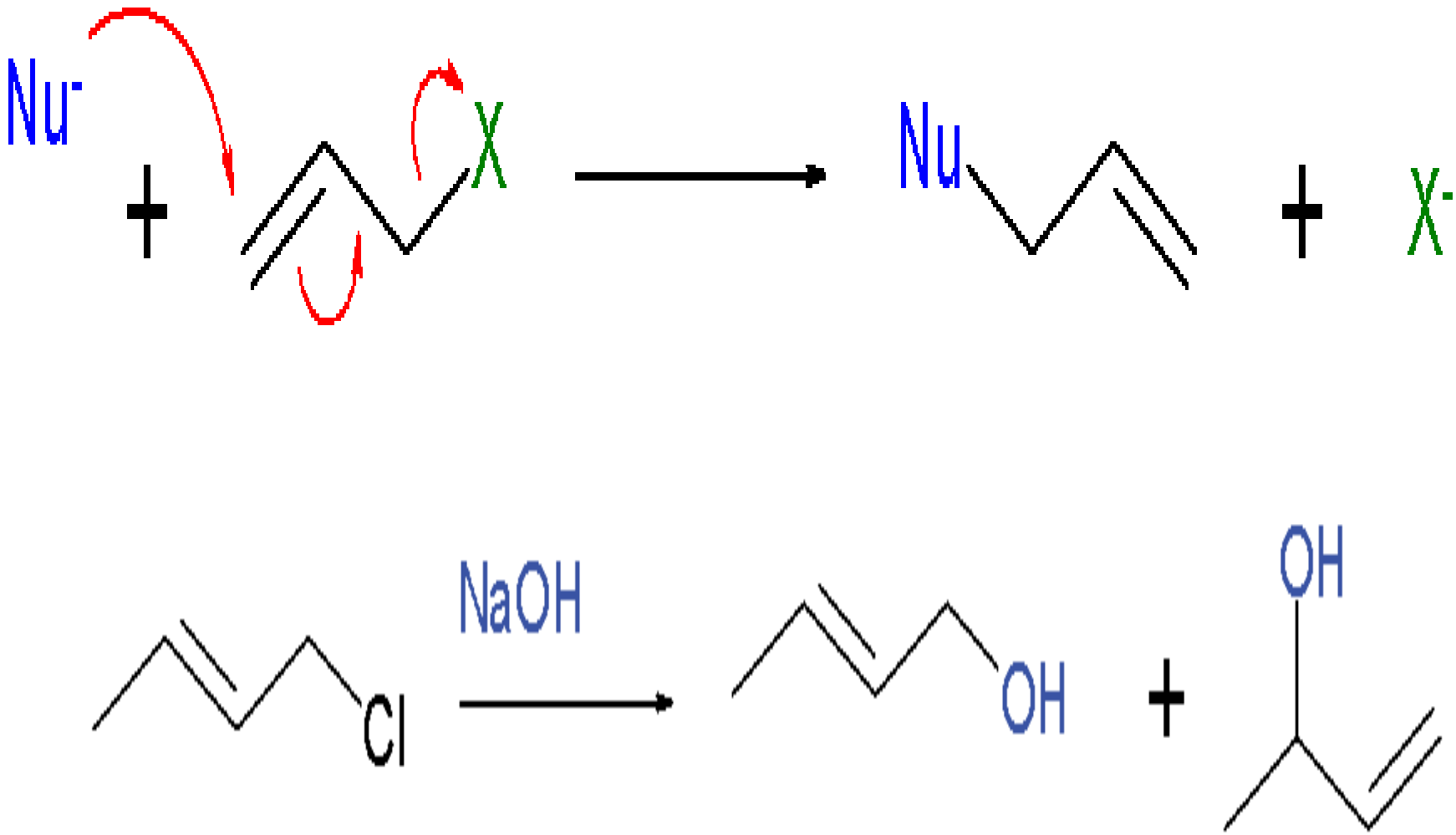

intramolecular
S_N2 reaction
intermolecular
S_N2 reaction

allylic rearrangement

- An **allylic rearrangement** or **allylic shift** is an organic reaction in which the double bond in an allyl chemical compound shifts to the next carbon atom. It is encountered in nucleophilic substitution
- In reaction conditions that favor a S_N1 reaction mechanism, the intermediate is a carbocation for which several resonance structures are possible. This explains the product distribution (or **product spread**) after recombination with nucleophile Y. This type of process is called an **S_N1' substitution**.

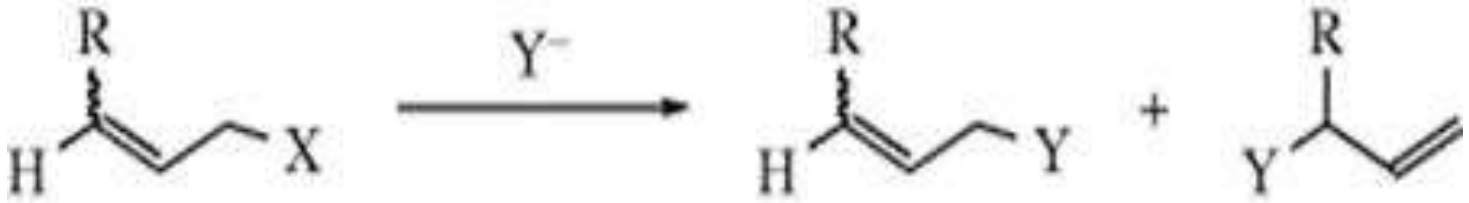
- Alternatively, it is possible for nucleophile to attack directly at the allylic position, displacing the leaving group in a single step, in a process referred to as **S_N2' substitution**. This is likely in cases when the allyl compound is unhindered, and a strong nucleophile is used. The products will be similar to those seen with S_N1' substitution. Thus reaction of 1-chloro-2-butene with sodium hydroxide gives a mixture of 2-buten-1-ol and 3-buten-2-ol:

- Nevertheless, the product in which the OH group is on the primary atom is minor. In the substitution of 1-chloro-3-methyl-2-butene, the secondary 2-methyl-3-buten-2-ol is produced in a yield of 85%, while that for the primary 3-methyl-2-buten-1-ol is 15%.


Nu-
X
Nu
X-
NaOH
Cl
OH
OH

- Allylic substrates rapidly undergo nucleophilic substitution reactions, but we discuss them in a separate section because they are commonly accompanied by a certain kind of rearrangement known as an *allylic rearrangement*. When allylic substrates are treated with nucleophiles under S_N1 conditions, two products are usually obtained: the normal one and a rearranged one.

- two products are usually obtained: the normal one and a rearranged one.


R
H
X
Y⁻
R
H
Y
+
R
Y


R—CH=CH—CH₂ ⟷ R—CH—CH=CH₂

Nucleophilic Substitution at an Allylic Carbon

❖ Allylic substrates rapidly undergo nucleophilic substitution reactions .

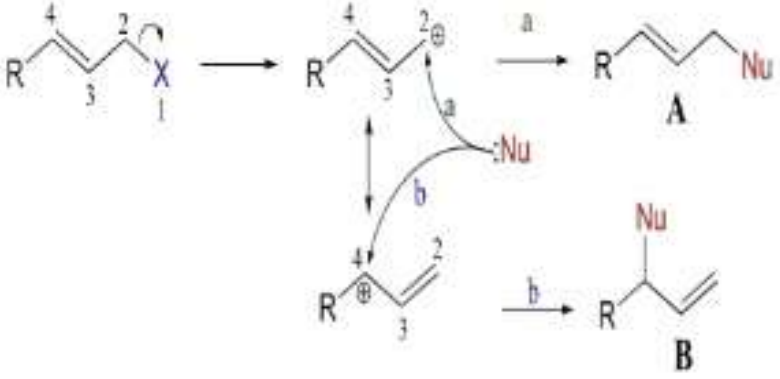
❖ usually accompanied by a certain kind of rearrangement known as an allylic rearrangement.

❖When allylic substrates are treated with nucleophiles under SN1 conditions, two products are usually obtained: the normal one and a rearranged one.

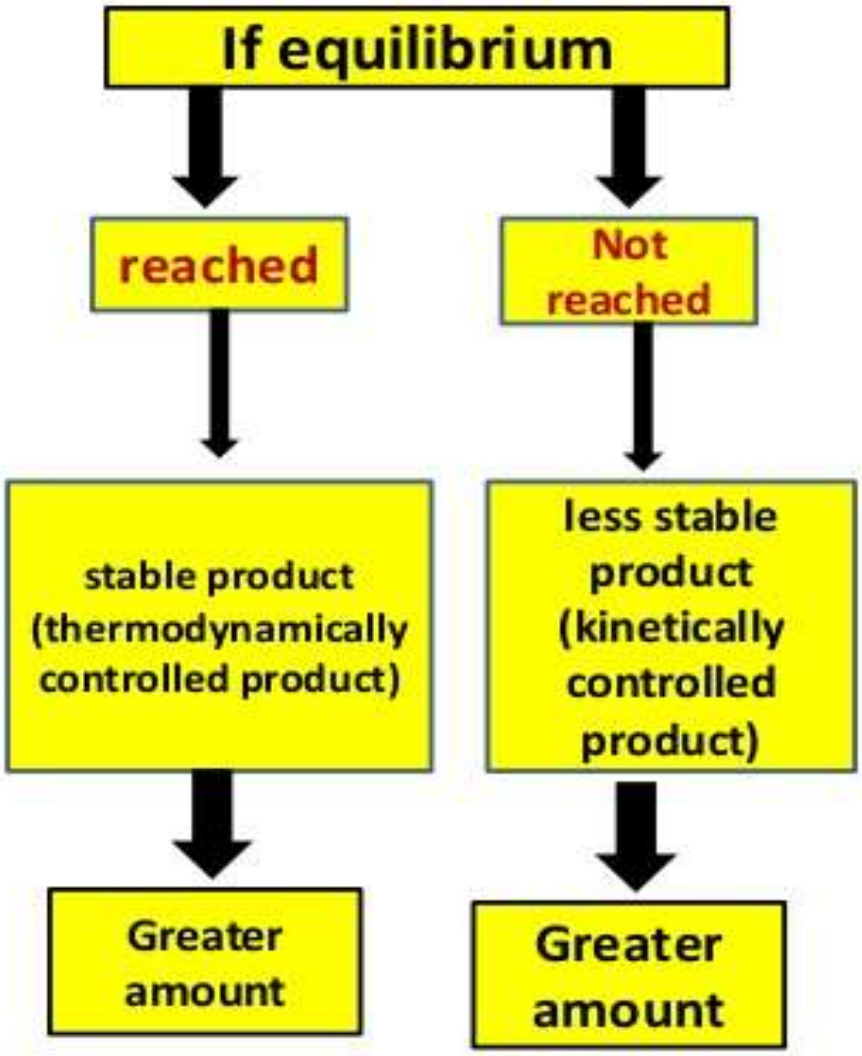
- **Reason-**

Two products are formed because an allylic type of carbocation is a resonance Hybrid so that C-1 and C-3 each carry a partial positive charge and both are attacked by nucleophile resulting in the formation of two products:

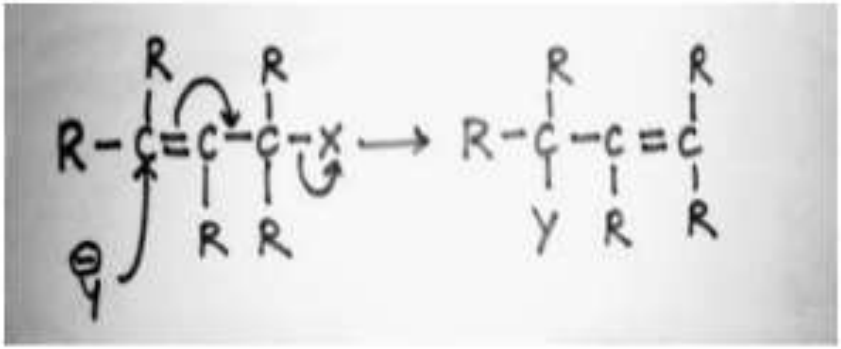
$$R\text{-}CH{=}CH\text{-}CH_2^+ \longleftrightarrow R\text{-}C^+H\text{-}CH{=}CH_2$$



- This mechanism has been called the SN1'mechanism.



- Nucleophilic substitution at an allylic carbon can also take place by an SN2 mechanism, in which case no allylic rearrangement usually takes place.
- In which the nucleophile attacks at the γ carbon rather than the usual position. This mechanism is called SN2' mechanism and is an allylic substitution. The SN2' mechanism takes place under SN2 conditions where α substation sterically retards the normal SN2 mechanism.



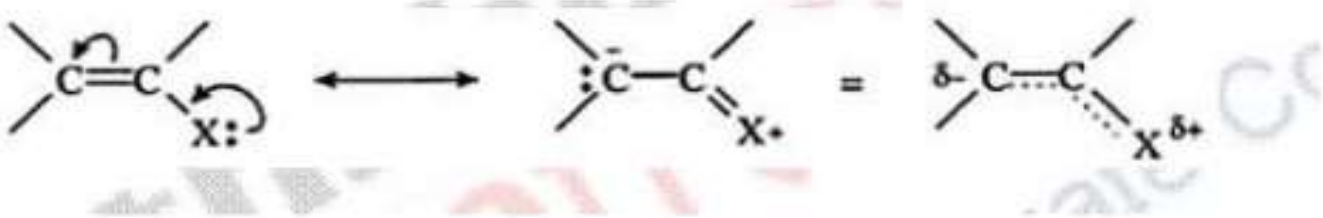
Nucleophilic Substitution at a Vinylic Carbon

➢Concerned with the nucleophilic substitution at unsaturated carbon such as vinylchloride (CH_2=CHCl).

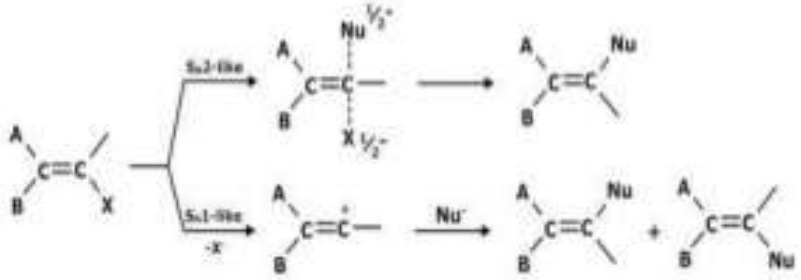
Nucleophilic substitution at a vinylic carbon is difficult under normal condition and is extremely slow compared to substitution at saturated carbon. The Vinyl chloride are essentially inert towards nucleophiles.

Reason-

1. Vinyl C-X bond (x= halogen, oxygen, nitogen) is stronger than the alkyl C-X bond because of a resonance interaction between the double bonds and an unsaturated pair on X. This interaction also weakens and polarizes the pi bond, which is why such compounds are reactive towards the electophilic addition.



2. The sn2 transition state as well as sn1 intermediate (a vinyl cation) are too high in energy to be readily accessible.

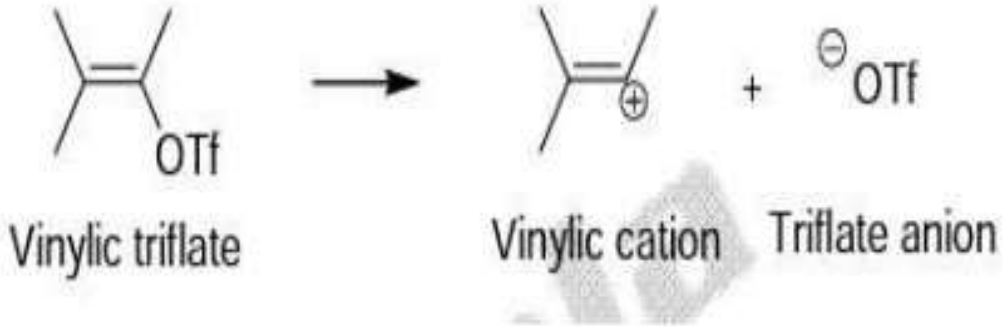


- Thus the rate determining step involves the breaking of C-X bond. The bond in vinyl halide is harder to break and reaction is slow.
- After a lot of reserch,
- The vinylic cation can readily made through by solvolysis of the SN1 kind if two conditions are met:

1. The leaving group is extremely good one.
2. The vinylic group contains electron releasing substituents.

- It takes 16-18 kcal more energy to break a C-X bond in vinyl halide than corresponding alkyl halide.

Most commonly used for this purpose is the *super leaving group – trifluro methanesulfonate (-OSO2CF3) WHICH is known as TRIFLATE*.

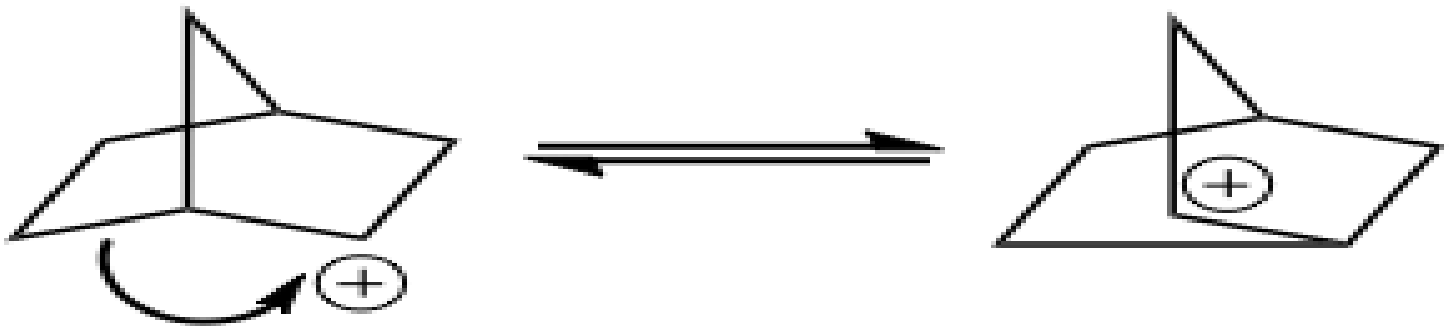


The powerful electron withdrawing F- ATOM(through dispersial of negative charge) help to stabalise the triflate anion, and makes the parent acid CF3SO2OH one of the strongest LOWRY- BRONSTED ACID known, much stronger than known H2SO4 AND HClO4.

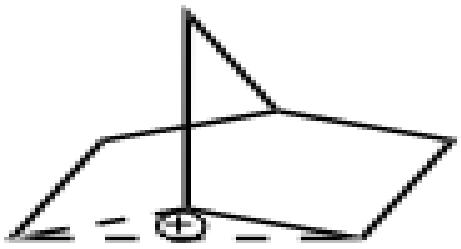
non-classical carbocation

- classical ion has a carbon with a sextet of electrons and 3 other bonds. The non-classical ion, on the other hand, involves 3 carbons with 2 electrons spread over them. This is called a 3-center 2-electron bond (hypercoordinate bonding) and is **a clear marker for a non-classical ion**.

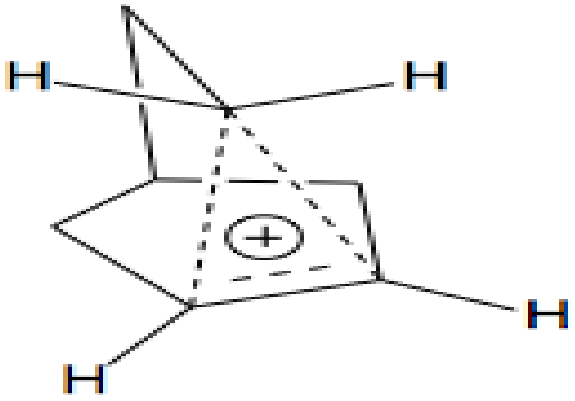
classical

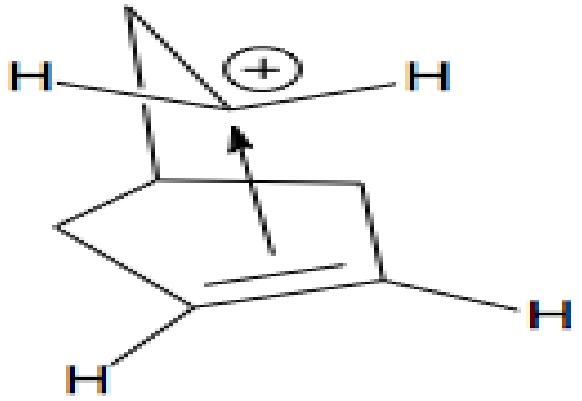


non-classical

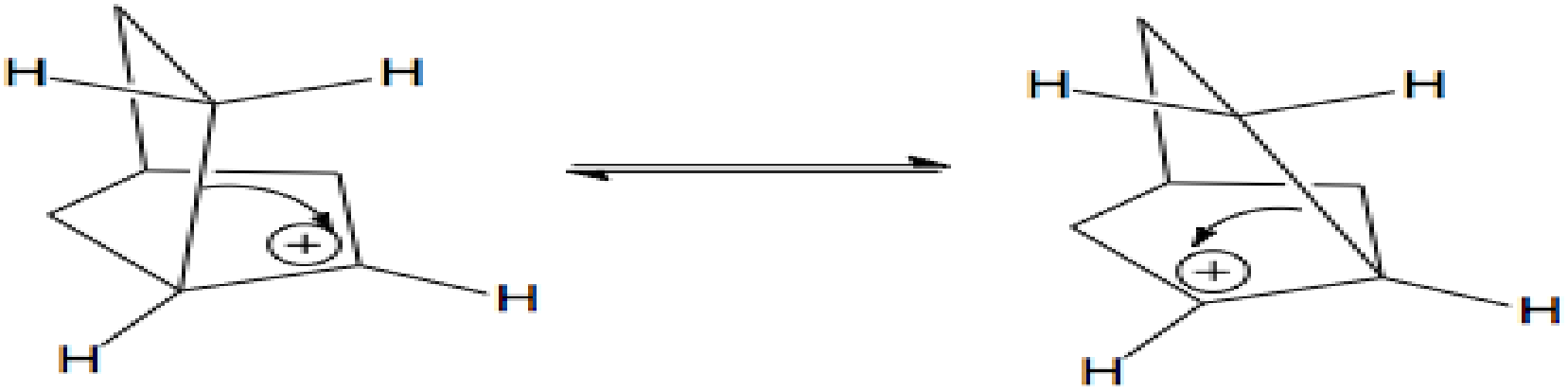


non-classical





classical



What is the Difference Between Classical and Nonclassical carbocation?

- We can classify carbocations into two groups as classical and nonclassical carbocations, depending on the chemical structure. The key difference between classical and nonclassical carbocation is that classical carbocations have a carbon atom having six electrons in three chemical bonds, whereas nonclassical carbocations have three-center two-electron structure. The energy of nonclassical carbocation is higher than the energy of classical carbocation, but the difference between these energies is very small; hence, it is very difficult to distinguish the difference between classical and nonclassical structures.

TOPIC

AROMATIC NUCLEOPHILIC SUBSTITUTION

- S_N1AR MECHANISM
- S_N1 MECHANISM
- BENZYNE MECHANISM
- IPSO,CINE SUBSTITUTION

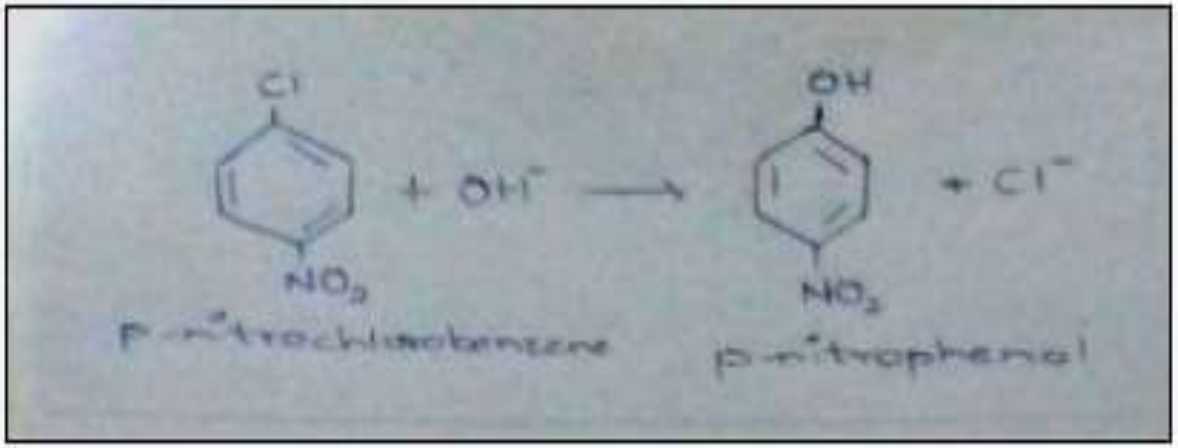
Aromatic Nucleophilic Substitution

- Under normal conditions, aryl halides do not undergo nucleophilic substitution reactions. They are less reactive towards the substitution reactions by nucleophile due to the following reasons:

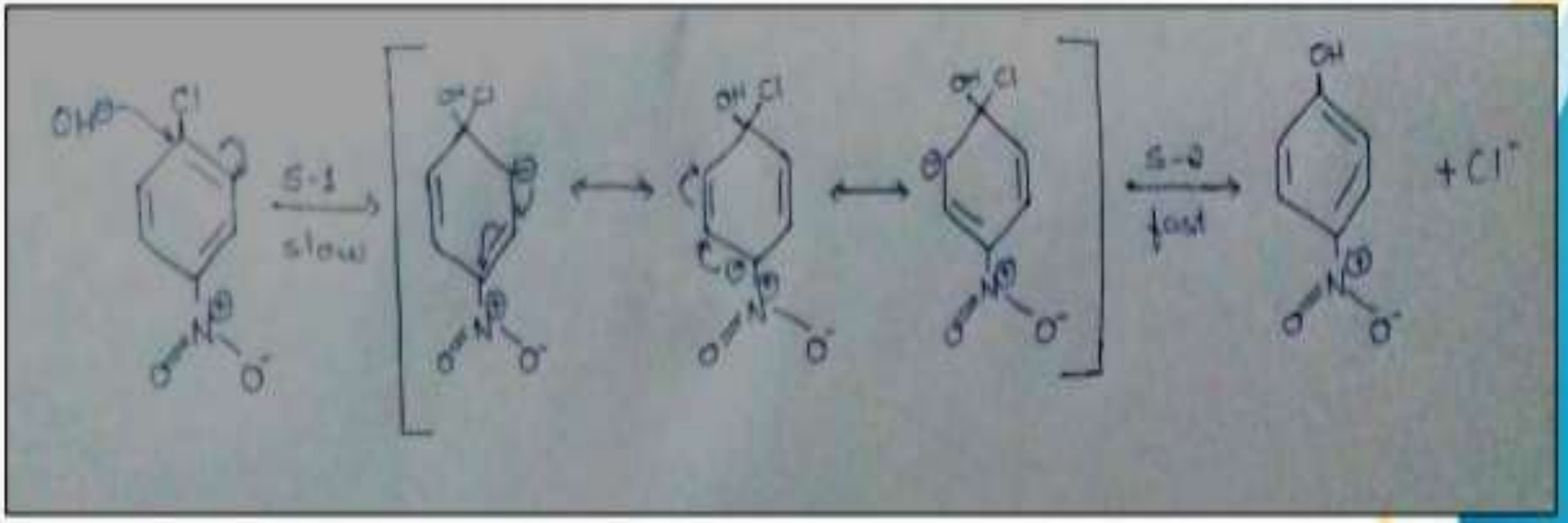
1. In case of alkyl halides, the carbon of C-X bond is sp^3 hybridised and its bond length of 177pm. In aryl halides, carbon of C-X bond is sp^2 hybridised and its bond length of 170pm. Shorter the bond length stronger is the bond and greater energy will be required to break the bond.
2. The lone pair of electrons of halogen atom in aryl halides is in conjugation with π-electrons of the ring.
3. Due to the resonance, the C-X bond in aryl halides possesses double bond character.

S_NAr mechanism

- Aryl halides does not undergo this mechanism easily because of the conjugation between lone pair of electrons on Cl and the C-atom in the ring.
- But if there is a strong withdrawing group in the ring such as nitro ($-NO_2$) group then it would undergo the reaction readily.
- It's important that the withdrawing group must be present either at ortho or para-position. As the resonating structures do not have negative charge at meta-position, hence the presence of withdrawing group on meta-position has no effect on reactivity.

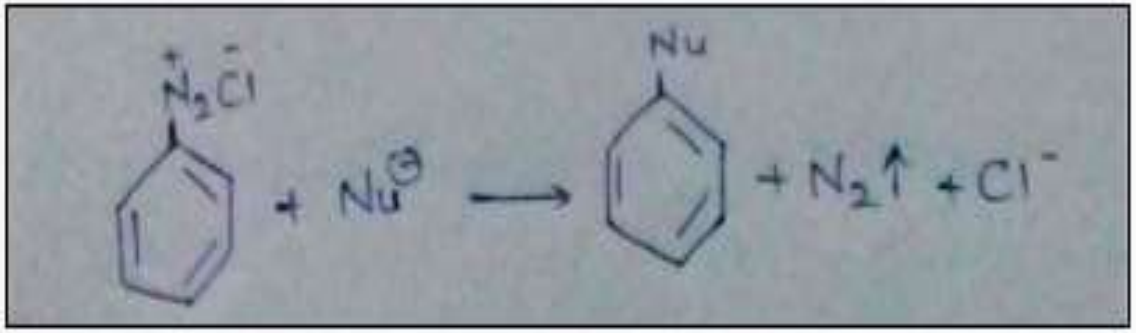

Cl
NO2
+ OH⁻
OH
NO2
+ Cl⁻
P-nitrochlorobenzene
p-nitrophenol

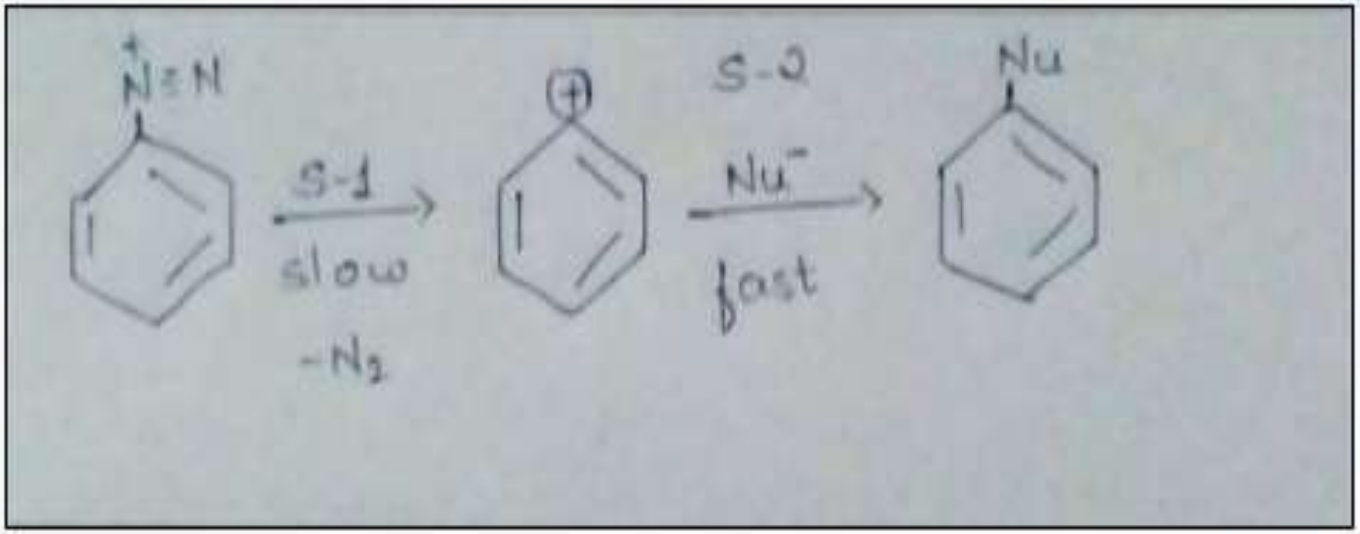
MECHANISM

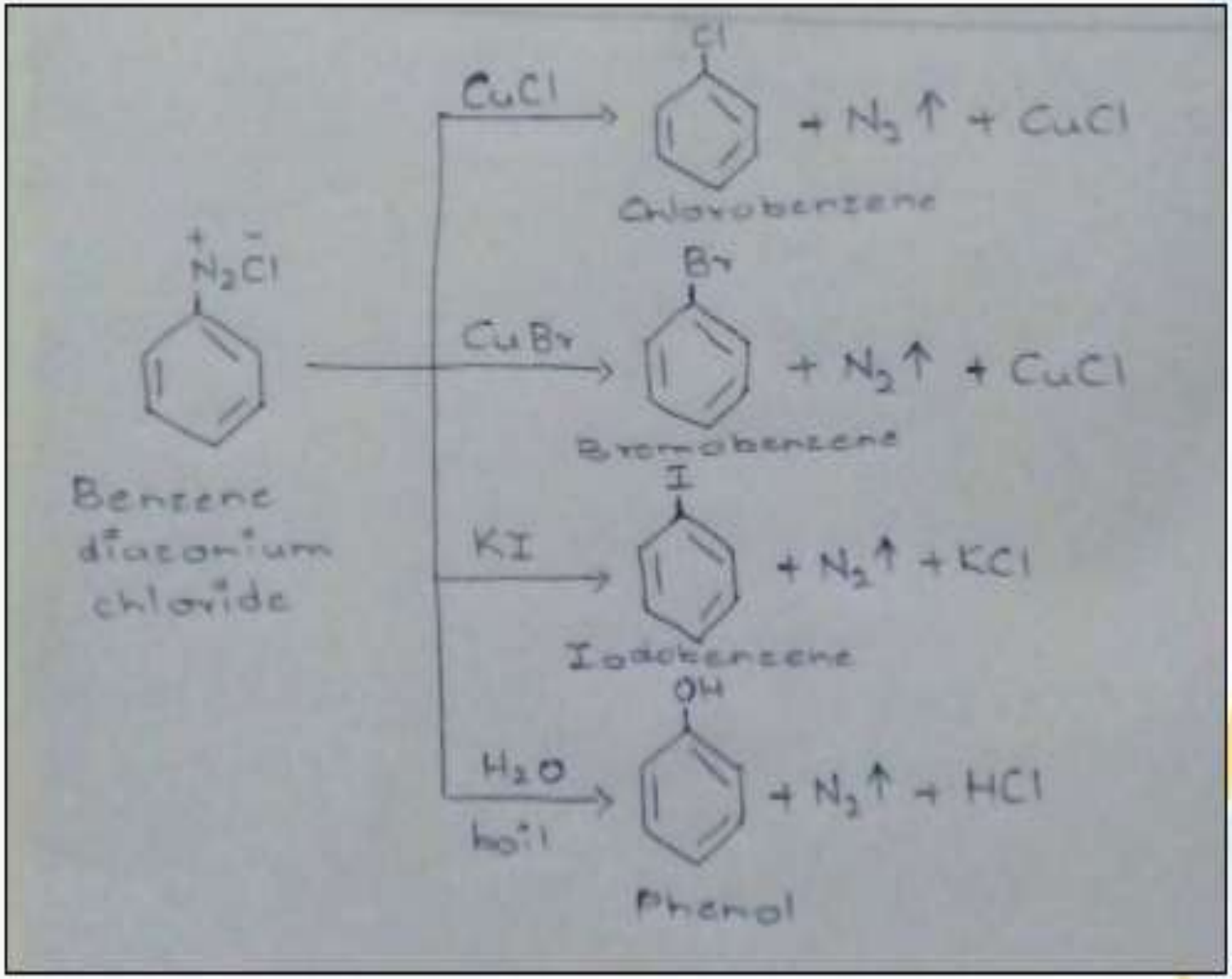

OH⊖
Cl
S-1
slow
OH
Cl
S-2
fast
+ Cl⁻

S_N1 mechanism

- It is very rare mechanism in aromatic compounds and is observed in Benzene diazonium compounds.
- As you know, it is a two step mechanism and the rate is independent of the nucleophile.

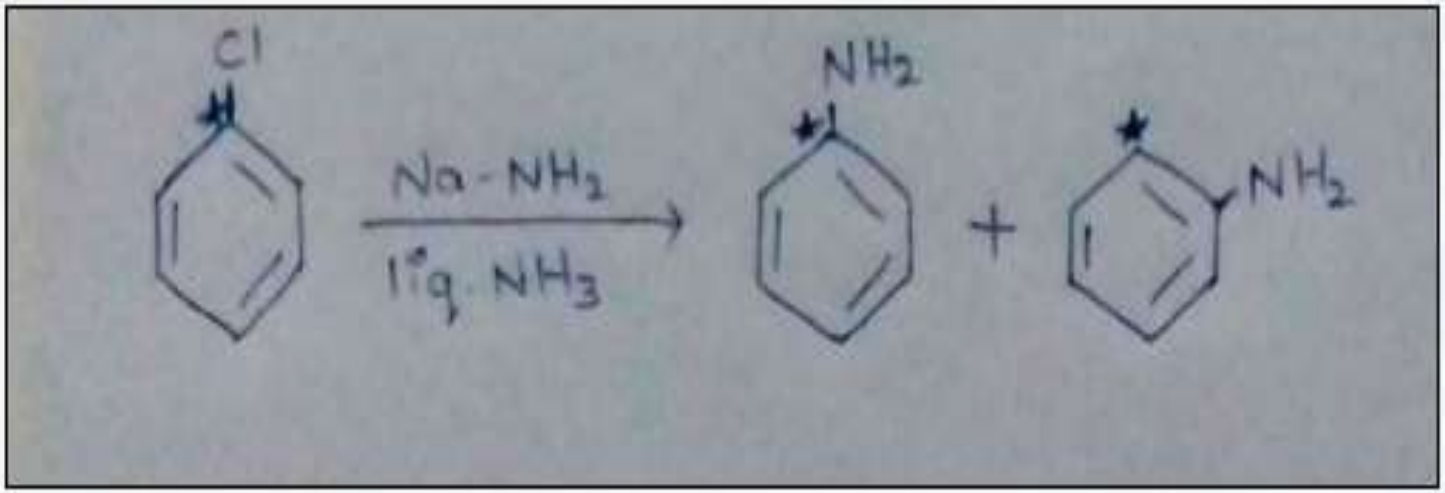



N≡N
S-1
slow
-N2
S-2
Nu⁻
fast
Nu


Cl
CuCl
+ N₂↑ + CuCl
Chlorobenzene
+N₂Cl⁻
Br
CuBr
+ N₂↑ + CuCl
Bromobenzene
Benzene diazonium chloride
I
KI
+ N₂↑ + KCl
Iodobenzene
OH
H₂O
boil
+ N₂↑ + HCl
Phenol

Benzyne mechanism

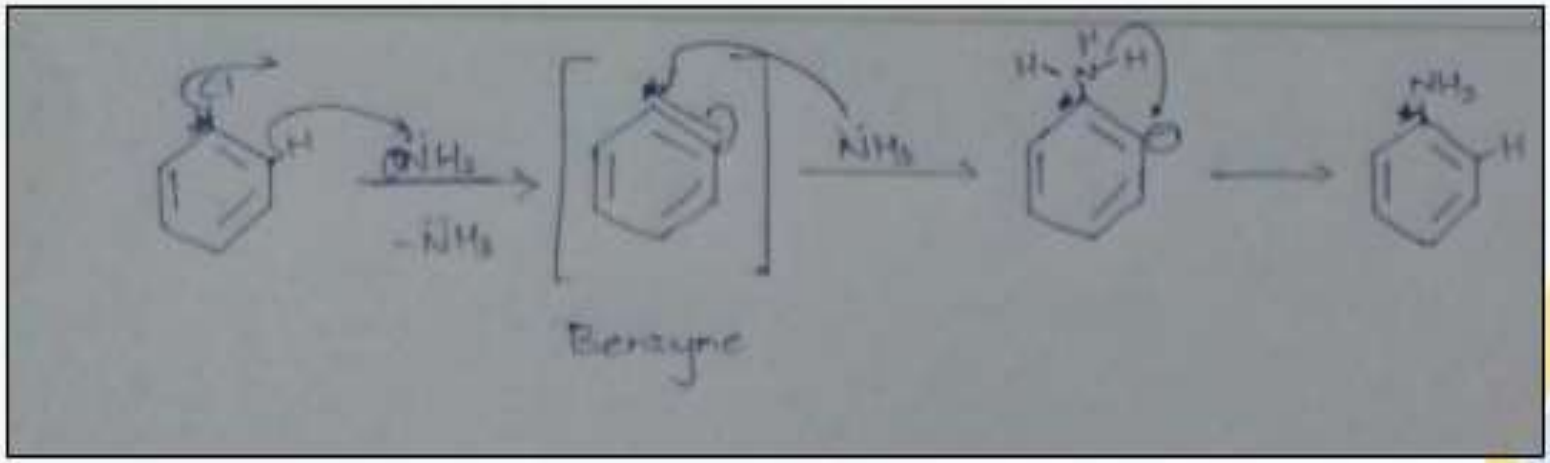
- It is also known as S_NEA mechanism as elimination and addition reaction occurs.
- It would not be easy to remove the chloride group from the ring due to conjugation between lone pair of electrons of chloride atom and carbon atom in the ring.
- It was possible in S_NAr mechanism due to presence of a strong withdrawing group.
- So here, the adjacent H-atom in the ring is used for the reaction.

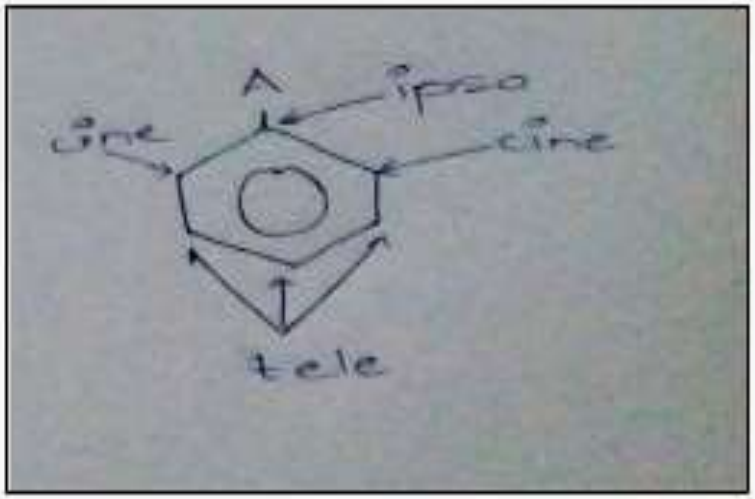


Here, we are using $C_{14,}$ radioactive isotope of carbon.

Two products are produced here, one is directly or ipso substituted product and the other is cine substituted product (direct= on the same position and cine=adjacent position).

MECHANISM





Ipso = at the same position

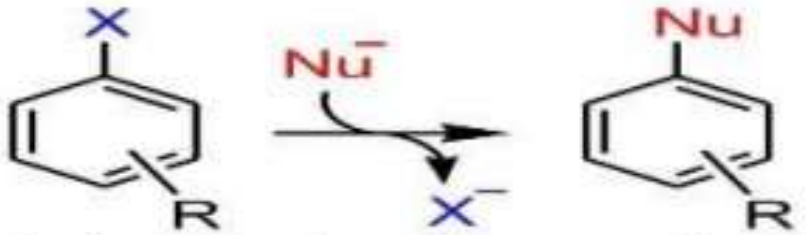
Cine= at the adjacent position (2,6)

Tele= more than 1 carbon atom far away from the leaving group (3,4,5)

What is NAS reaction:

- A **nucleophilic aromatic substitution** is substitution **reaction** in organic chemistry in which the **nucleophile** displaces a good leaving group, such as a halide, on an **aromatic** ring.
- Nucleophili aromatic substitution reaction can follow two very different path: the bimolecular displacement mechanism for activated aryl halide and elimination –edition

Mechanism which involve the remarkable intermediate called benzyne.



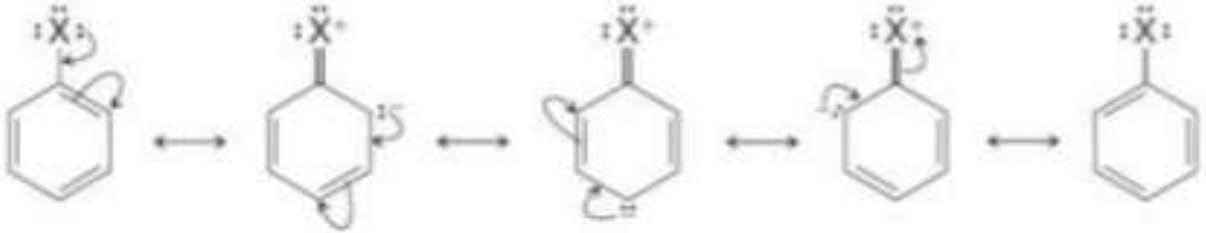
X = halogen etc. Nu = nucleophile

SNAr mechanism

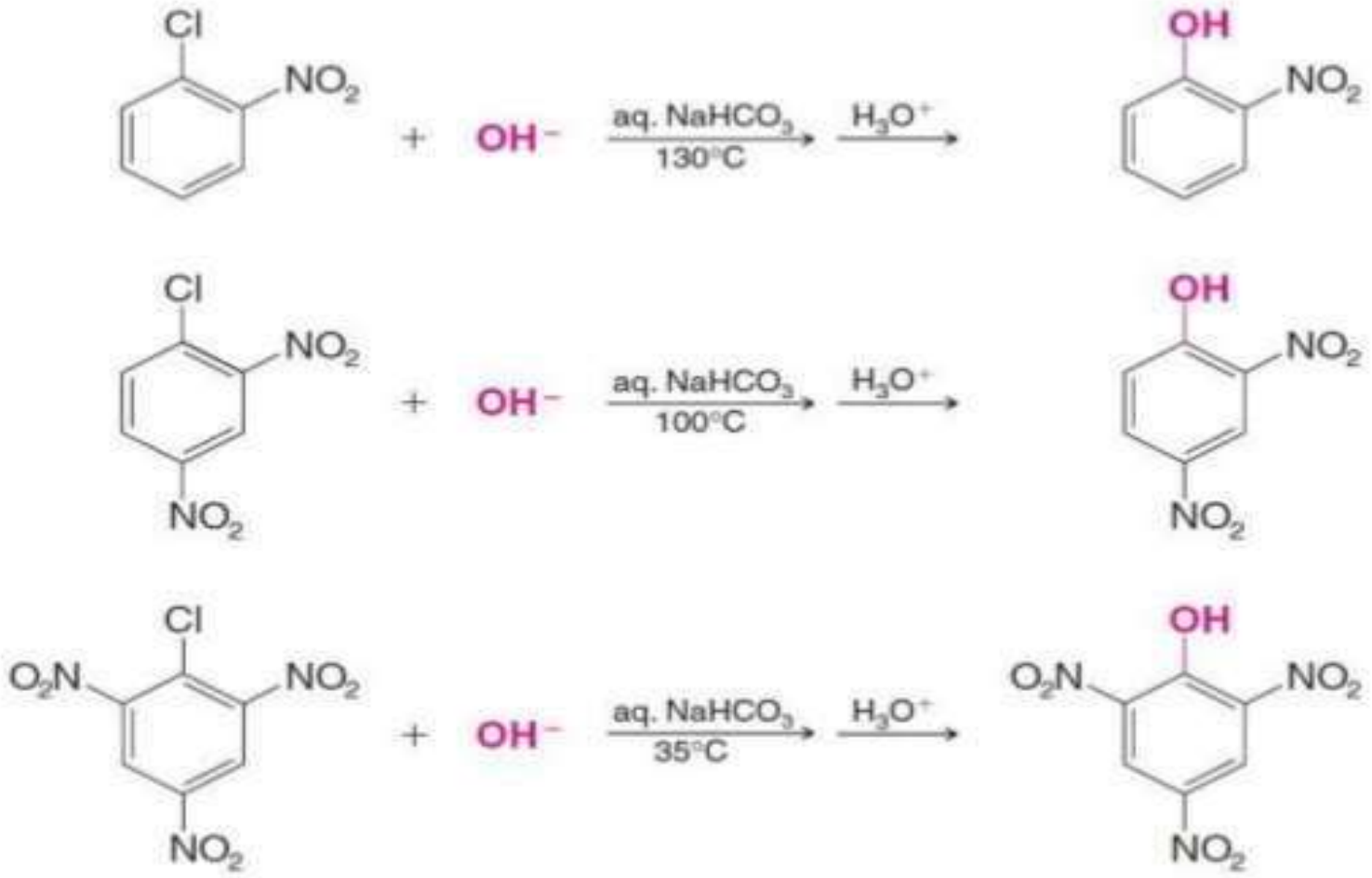
- Simple aryl halides, are relatively unreactive toward nucleophilic substitution under conditions that would give rapid nucleophilic substitution with alkyl halides.

Two effects make the carbon–halogen bonds of aryl halides shorter and stronger:

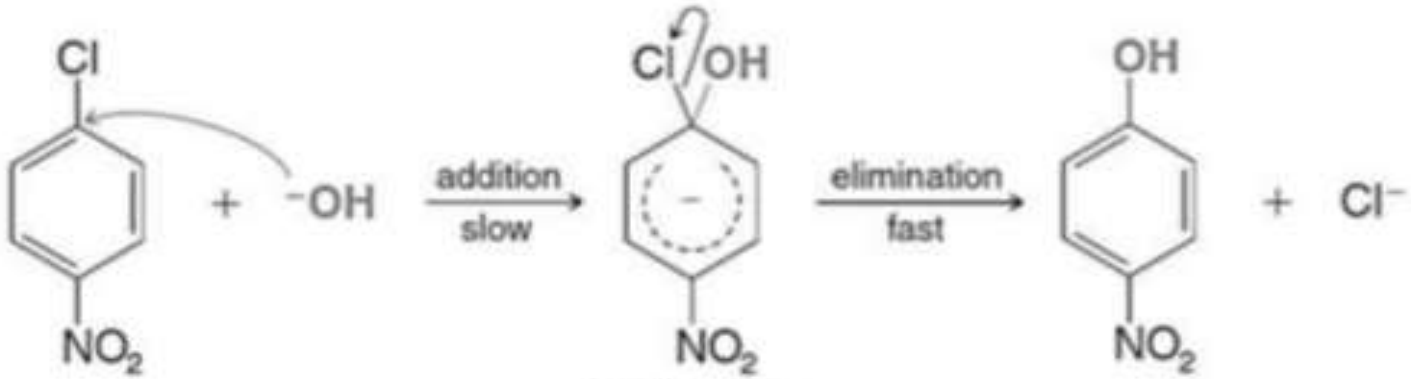
- The carbon of halide is sp2 hybridized, and therefore the electrons of the carbon orbital are closer to the nucleus than those of an sp3-hybridized carbon.
- Resonance strengthens the carbon–halogen bond by giving it double-bond character:



In presence of an electron withdrawing group



Mechanism



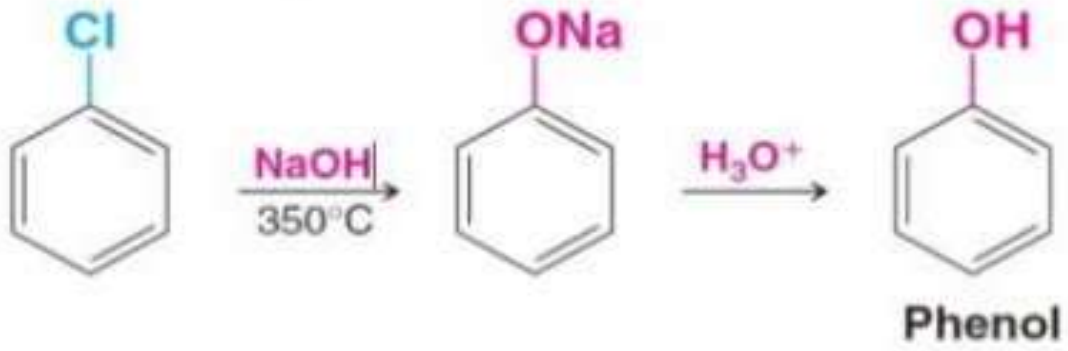
Carbanion
(Meisenheimer intermediate)

S_N1 MECHANISM

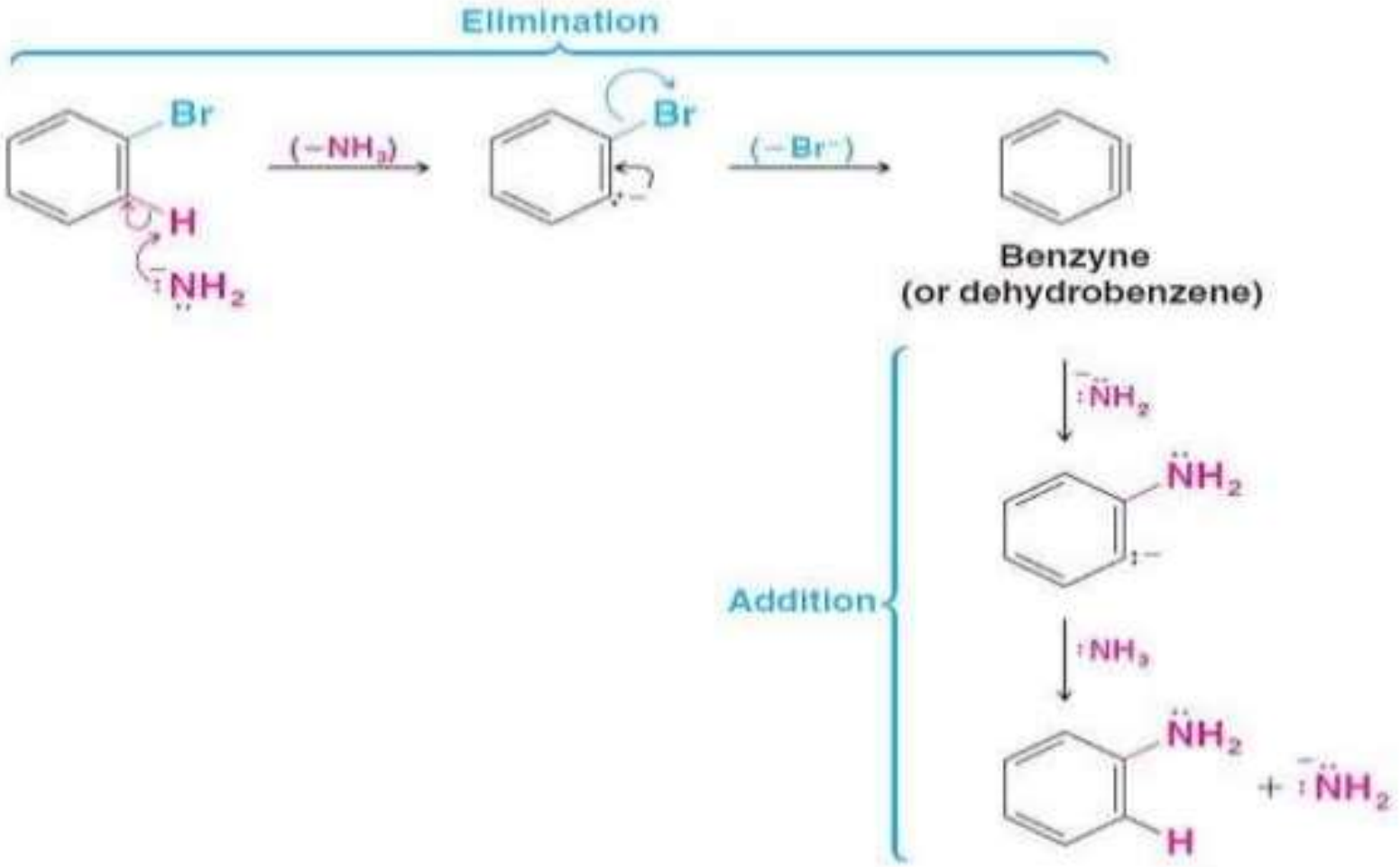
- THE AROMATIC S_N1 MECHANISM ENCOUNTERED WITH DIAZONIUM SALTS ONLY.

Benzyne Mechanism

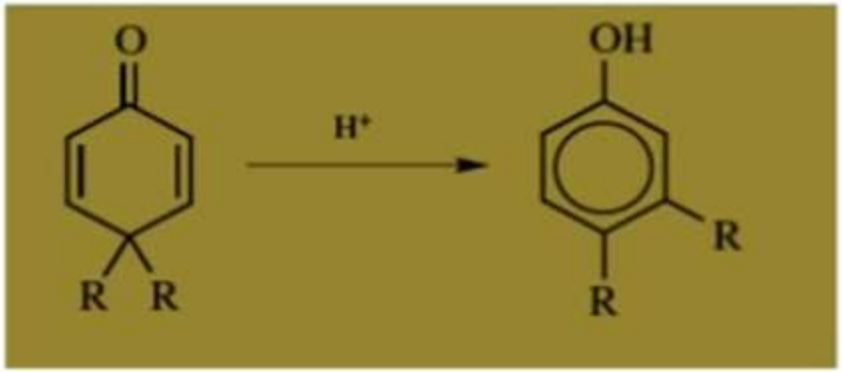
Although aryl halides such as chlorobenzene and bromobenzene do not react with most nucleophiles under ordinary circumstances, they do react under highly forcing conditions. Chlorobenzene can be converted to phenol by heating it with aqueous sodium hydroxide in a pressurized reactor at 350°C.



Mechanism


Elimination
Br
H
$\ddot{N}H_2$
(−NH_3)
Br
(−Br^-)
Benzyne
(or dehydrobenzene)
Addition
$\ddot{N}H_2$
$\ddot{N}H_2$
NH_3
$\ddot{N}H_2$
H
+ $\ddot{N}H_2$

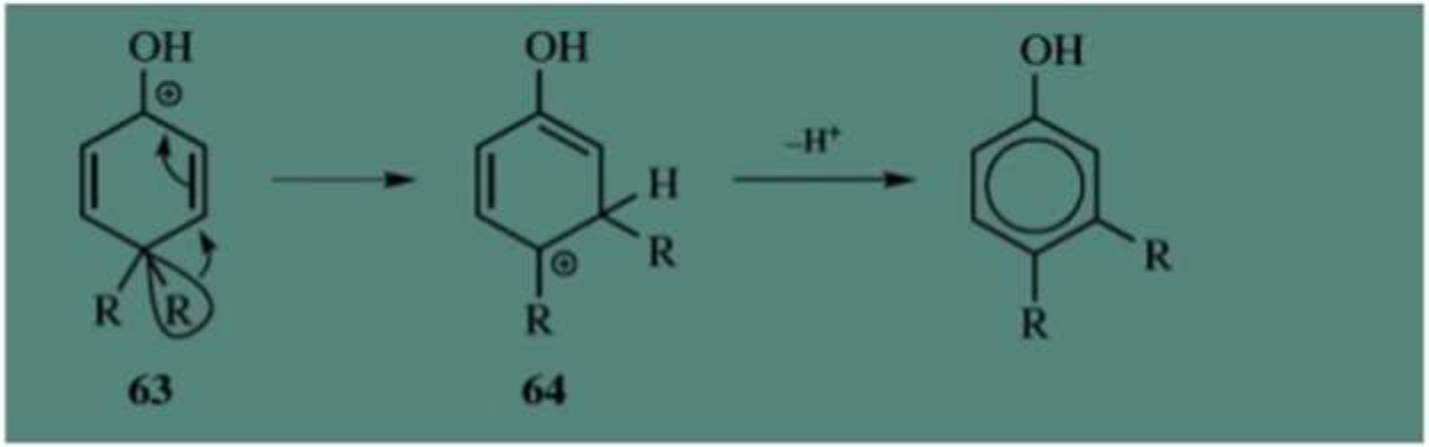
Dienone–Phenol Rearrangement



- Cyclohexadienone derivatives that have two alkyl groups in the 4 position undergo, on acid treatment,1,2 migration of one of these groups from 64 to give the phenol.

- Note that a photochemical version of this reaction has been observed

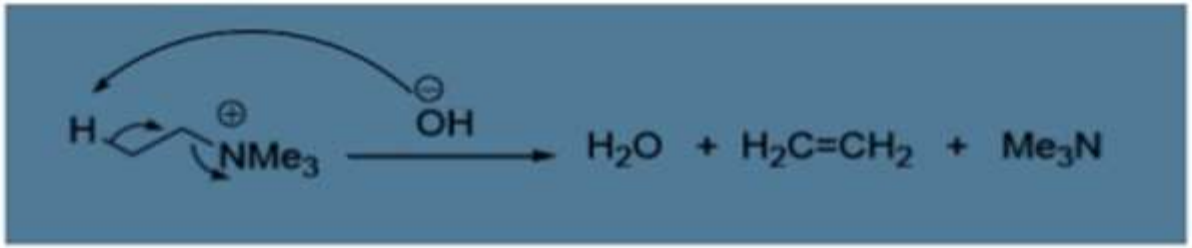
Mechanism



The driving force in the overall reaction (the dienone–phenol rearrangement) is of course creation of an aromatic system.

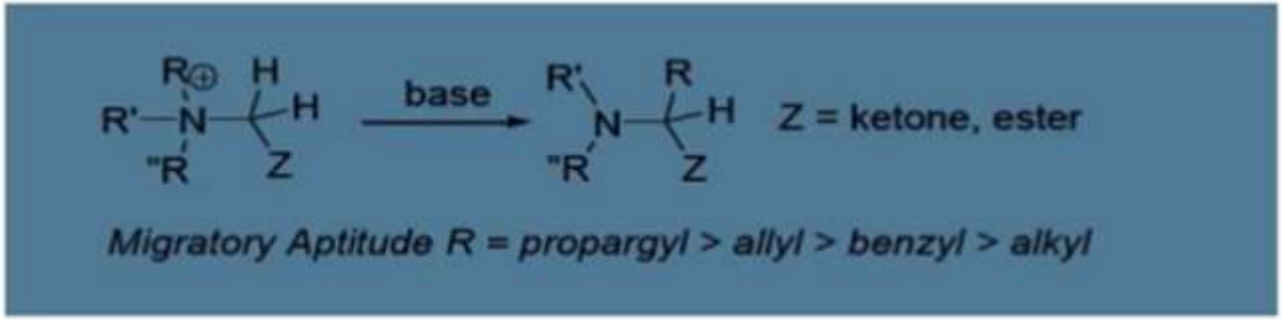
Stevens Rearrangement

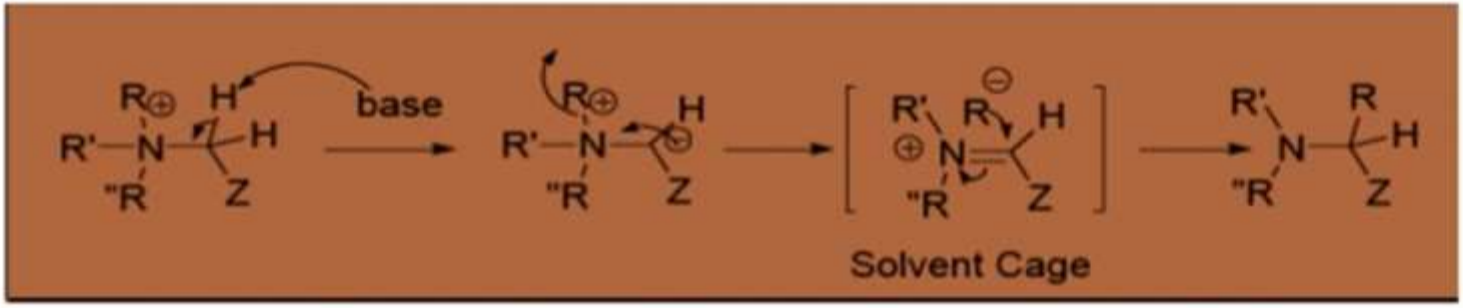
Quaternary ammonium salt which has β-hydrogen proceeds E2 (Hofmann) elimination with base.



Mechanism

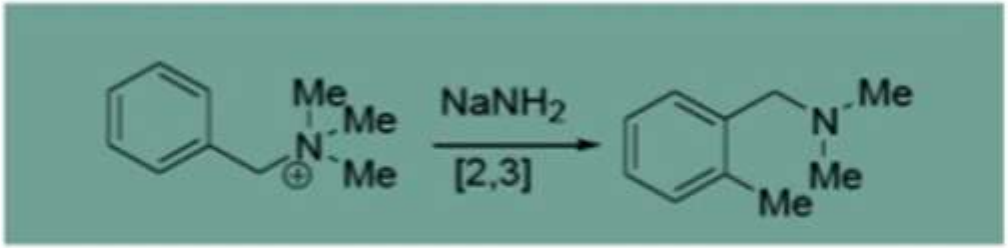
In case of quaternary ammonium salts containing β-ketone or ester or aryl group, an α- hydrogen is removed by base to give an ylide and then the rearrangement occurs.



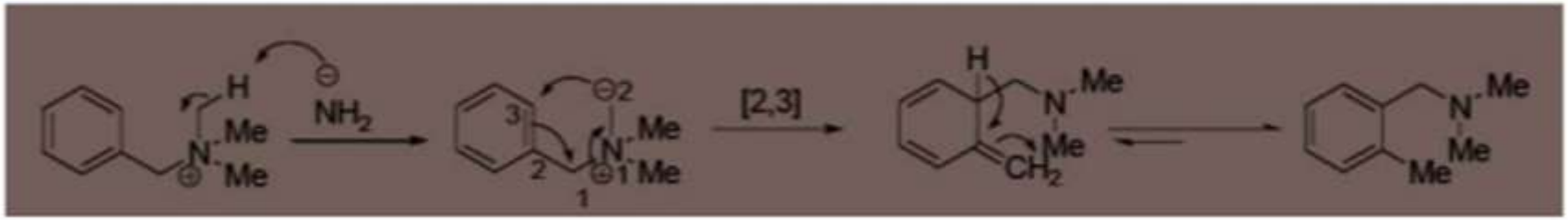


Sommelet-Hauser Rearrangement

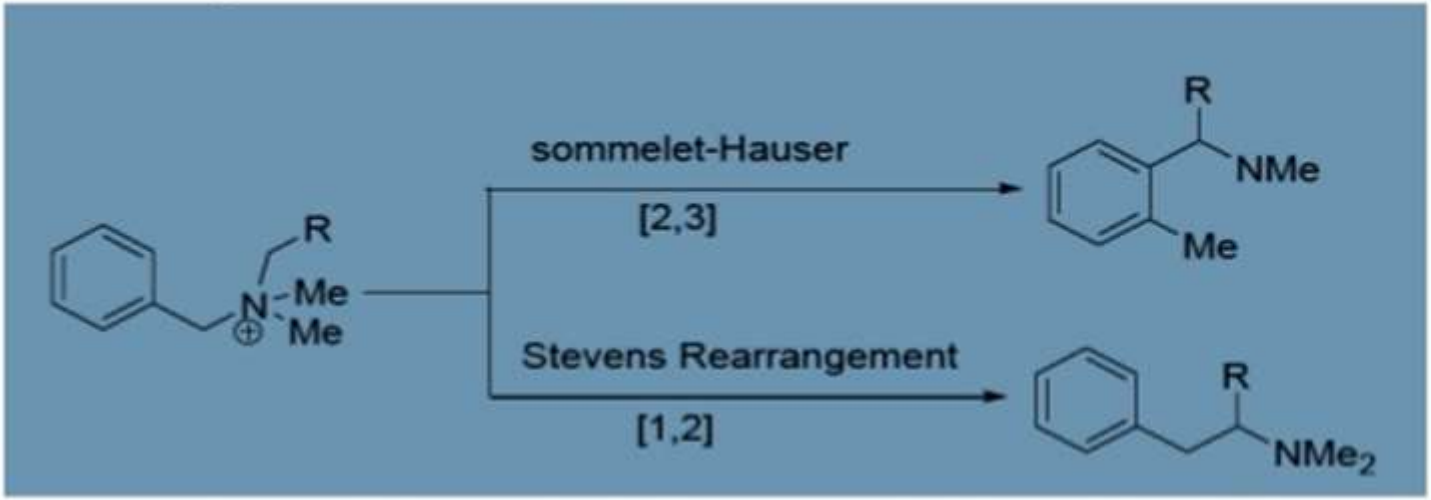
- In the absence of β-carbonyl group, the α-hydrogen is too weakly acidic for hydroxide ion induced rearrangement.
- Thus, a strong base, such as amide ion in liquid ammonia, is to be used, when the rearrangement takes a different course: instead of [1,2] shift (Steven's rearrangement), a [3,2]-sigma-tropic rearrangement takes place which is called Sommelet-Hauser rearrangement.



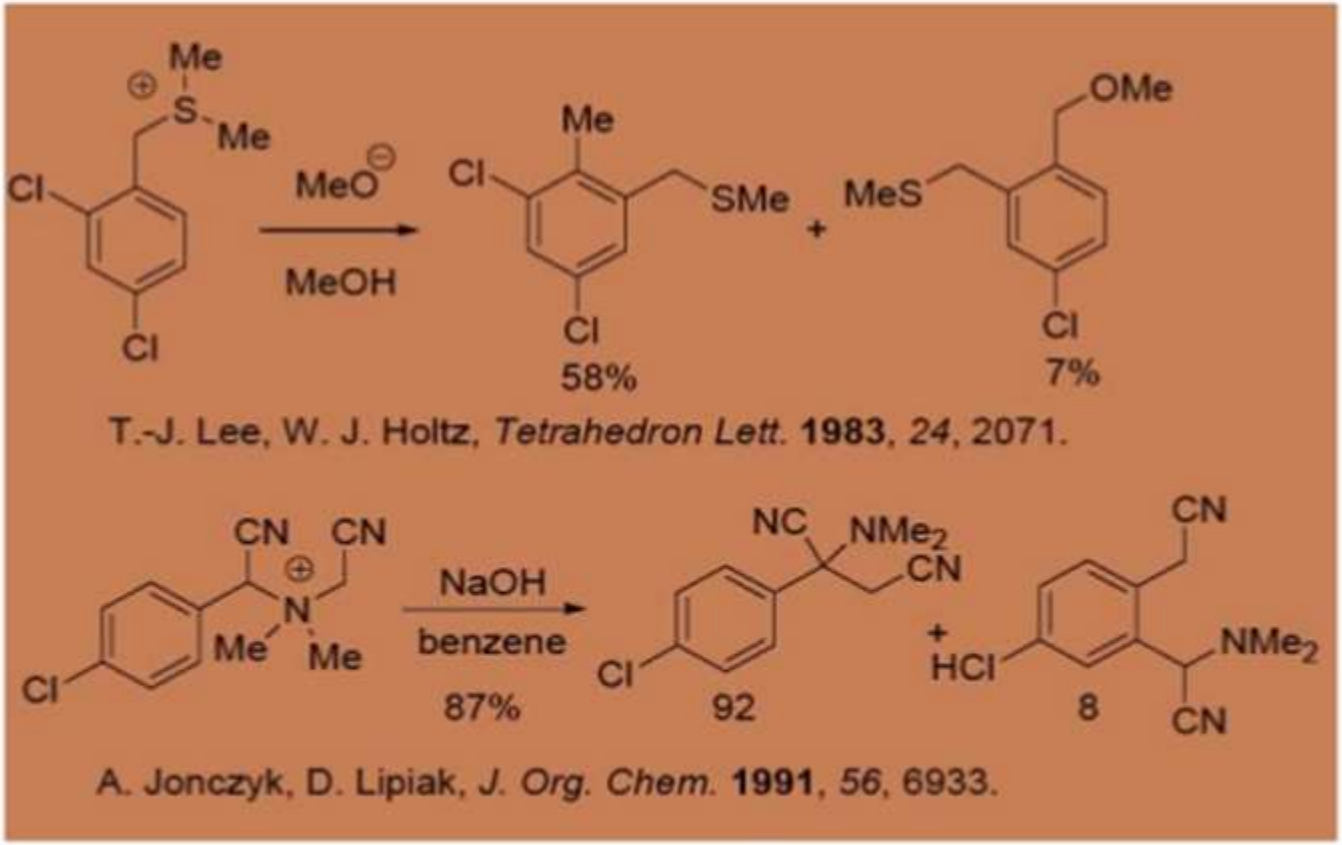
Mechanism



There can be competition between Stevens and Sommelet-Hauser rearrangement mechanisms.

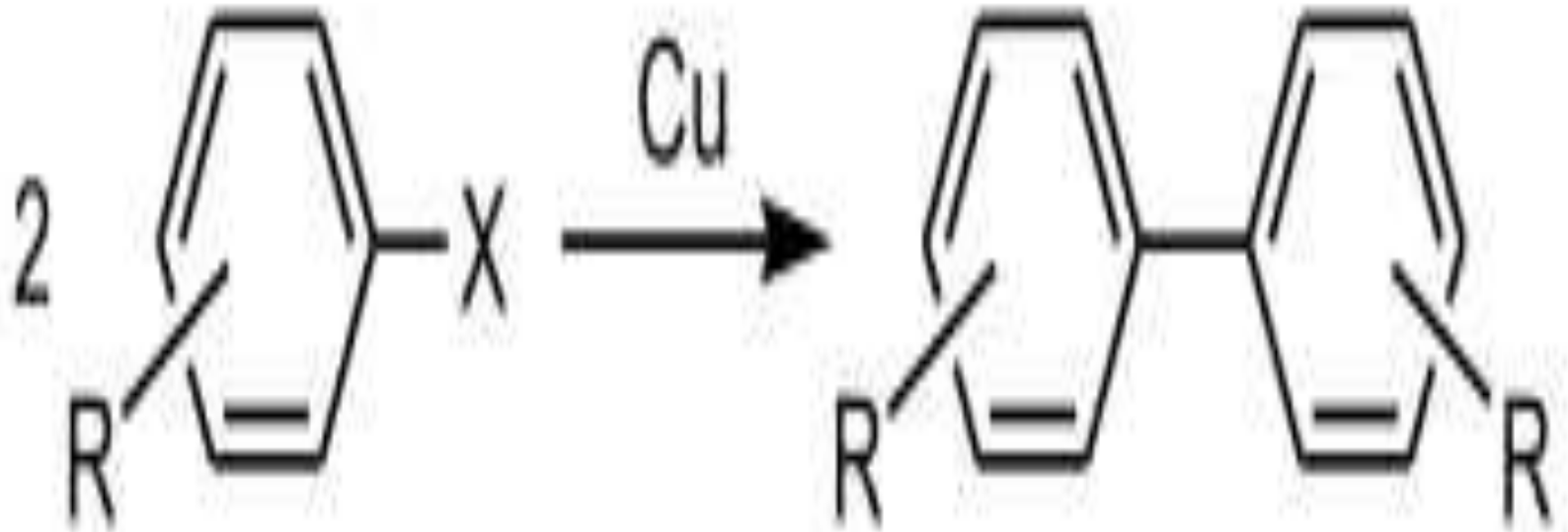


Examples


Me
S
Me
Cl
Cl
MeO
MeOH
Me
Cl
SMe
Cl
58%
+
OMe
MeS
Cl
7%
T.-J. Lee, W. J. Holtz, Tetrahedron Lett. 1983, 24, 2071.
CN
CN
N
Me
Me
Cl
NaOH
benzene
87%
NC
NMe2
CN
Cl
92
+
HCl
CN
NMe2
CN
8
A. Jonczyk, D. Lipiak, J. Org. Chem. 1991, 56, 6933.

Ullmann Reaction

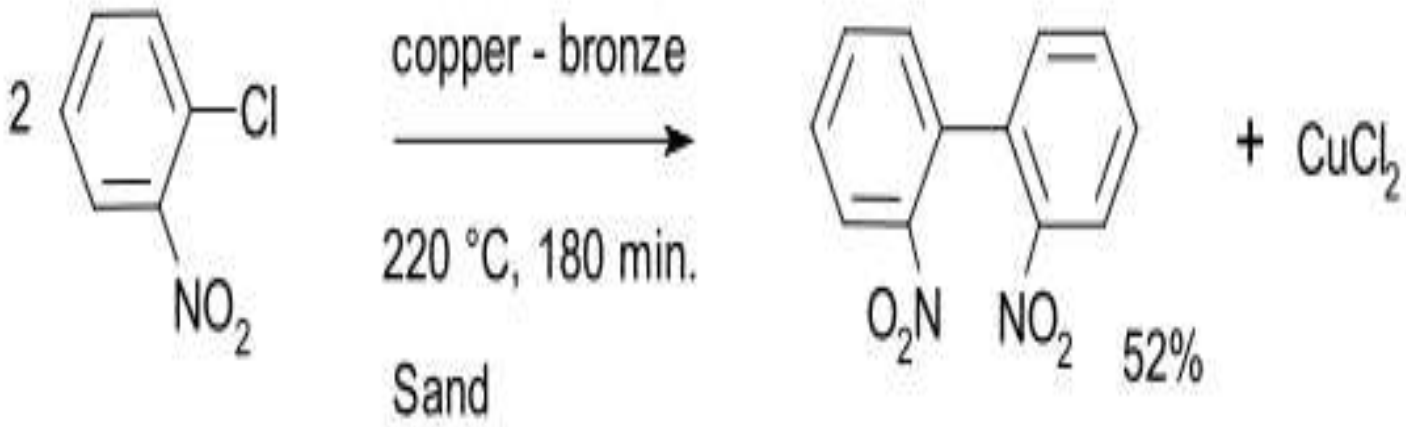
- The Ullmann reaction (also known as Ullmann coupling) is an organic named reaction that involves the coupling of two aryl halides in the presence of copper to yield a biaryl as the product. This coupling reaction is named after the German chemist Fritz Ullmann. The general format of the Ullmann reaction is illustrated below.



X = I, Br

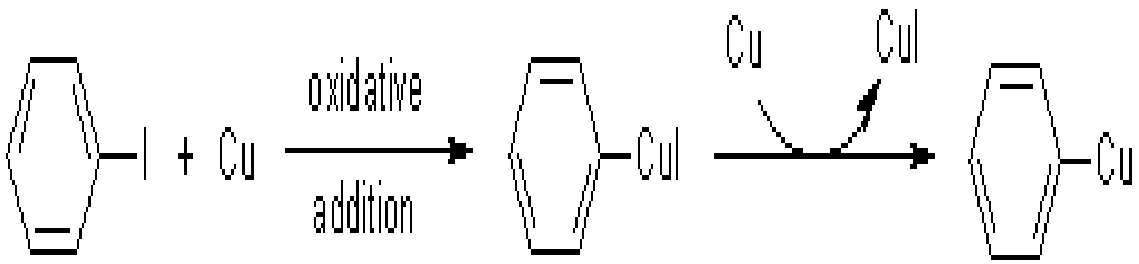
Ullmann reaction

- An illustration of the Ullmann reaction undergone by ortho-chloronitrobenzene in the presence of a copper-bronze alloy at a temperature of approximately 500 K to afford 2,2’-dinitrobiphenyl is provided below.

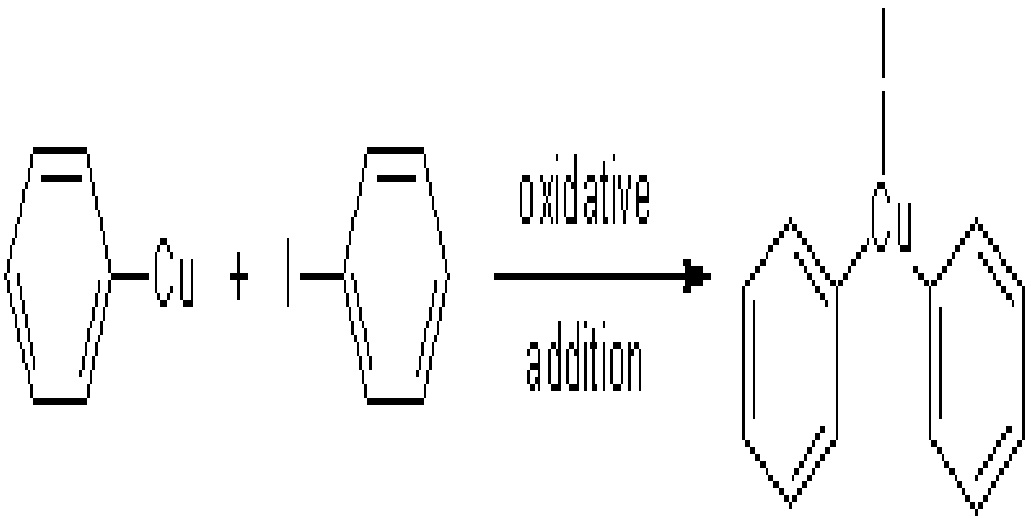

2
Cl
NO2
copper - bronze
220 °C, 180 min.
Sand
O2N
NO2
52%
+ CuCl2

Ullmann Reaction Mechanism

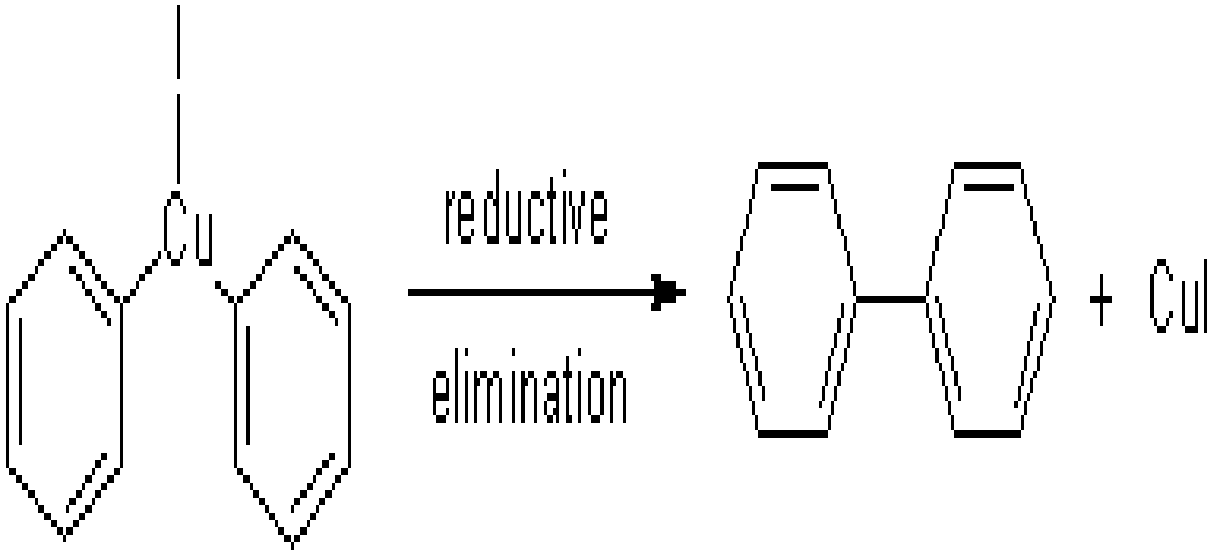
- **Step 1**
- The mechanism of the Ullmann reaction involves the formation of an active copper(I) species upon the introduction of the aryl halide to an excess of metallic copper under relatively high temperatures (>200^{o}C).


I
+ Cu
oxidative
addition
CuI
Cu
CuI
Cu

- **Step 2**
- This copper(I) species undergoes further oxidative addition with another haloarene molecule, linking the two molecules (as illustrated below).


Cu
oxidative
addition
Cu

- **Step 3**
- In the final step of the Ullmann reaction mechanism, the copper compound formed by the two aryl halide molecules undergoes reductive elimination, resulting in the formation of a new carbon-carbon bond between the two aryl compounds (as illustrated below).


Cu
reductive
elimination
+ CuI

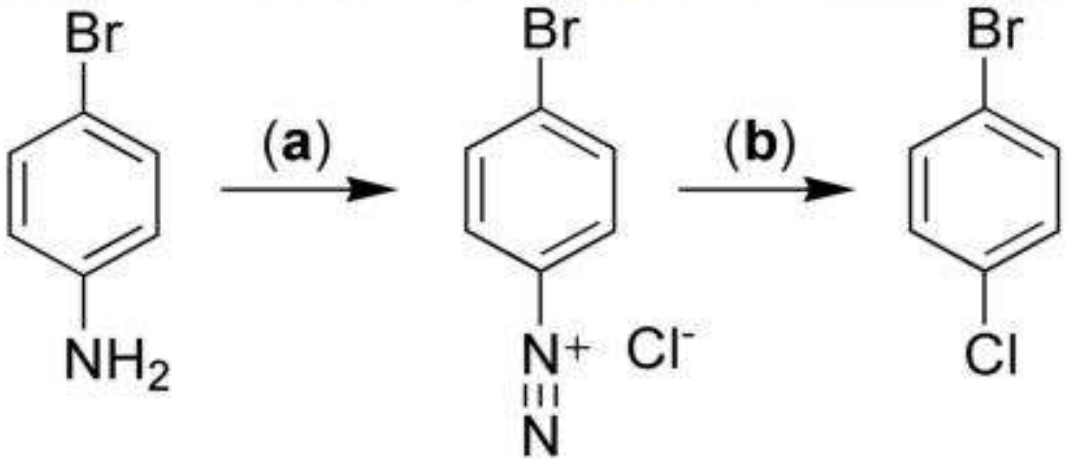
Applications of the Ullmann Reaction

- Biphenylenes can be obtained from 2,2-diiodobiphenyl via the Ullmann reaction.
- This reaction can also be employed for the closure of five-membered rings.
- An unsymmetrical reaction can also be achieved given that one of the reactants is provided in excess.
- Chiral reactants can be coupled into a chiral product via this reaction.

Sandmeyer Reaction

- Sandmeyer reaction is a type of substitution reaction that is widely used in the production of aryl halides from aryl diazonium salts. Copper salts like chloride, bromide, or iodide ions are used as catalysts in this reaction. Notably, Sandmeyer reaction can be used to perform unique transformations on benzene. The transformations include hydroxylation, trifluoromethylation, cyanation, and halogenation.

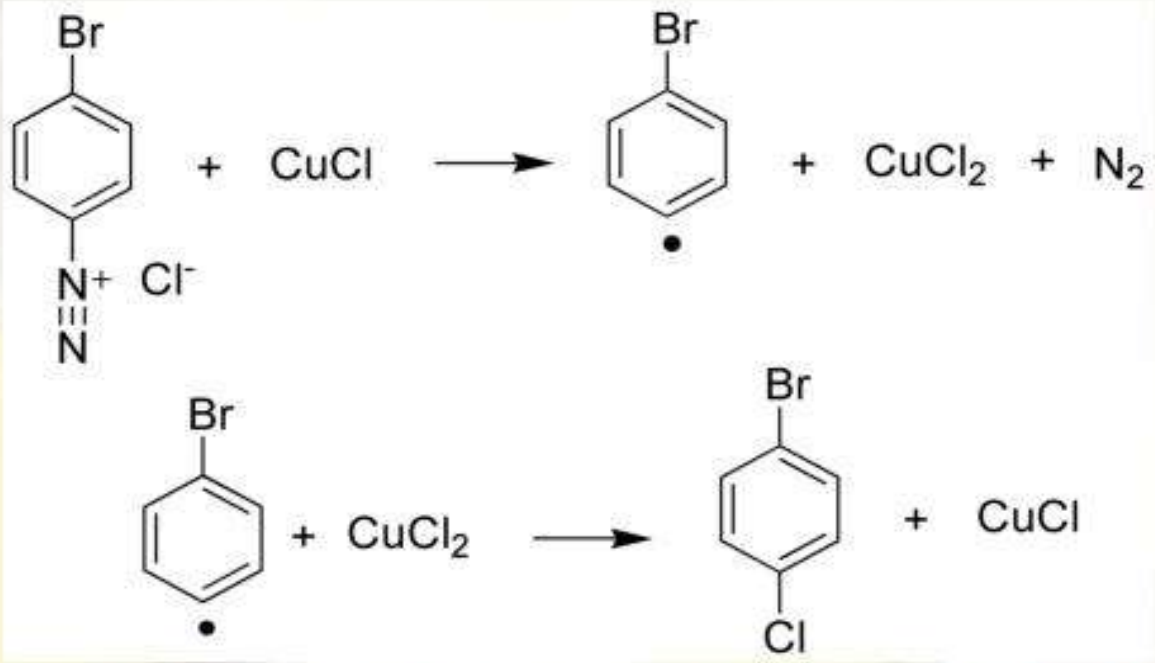
Purpose



(**a**) $NaNO_2$, HCl, 0°C, 5 min; (**b**) CuCl, 0°C to 70°C, 15-20 min

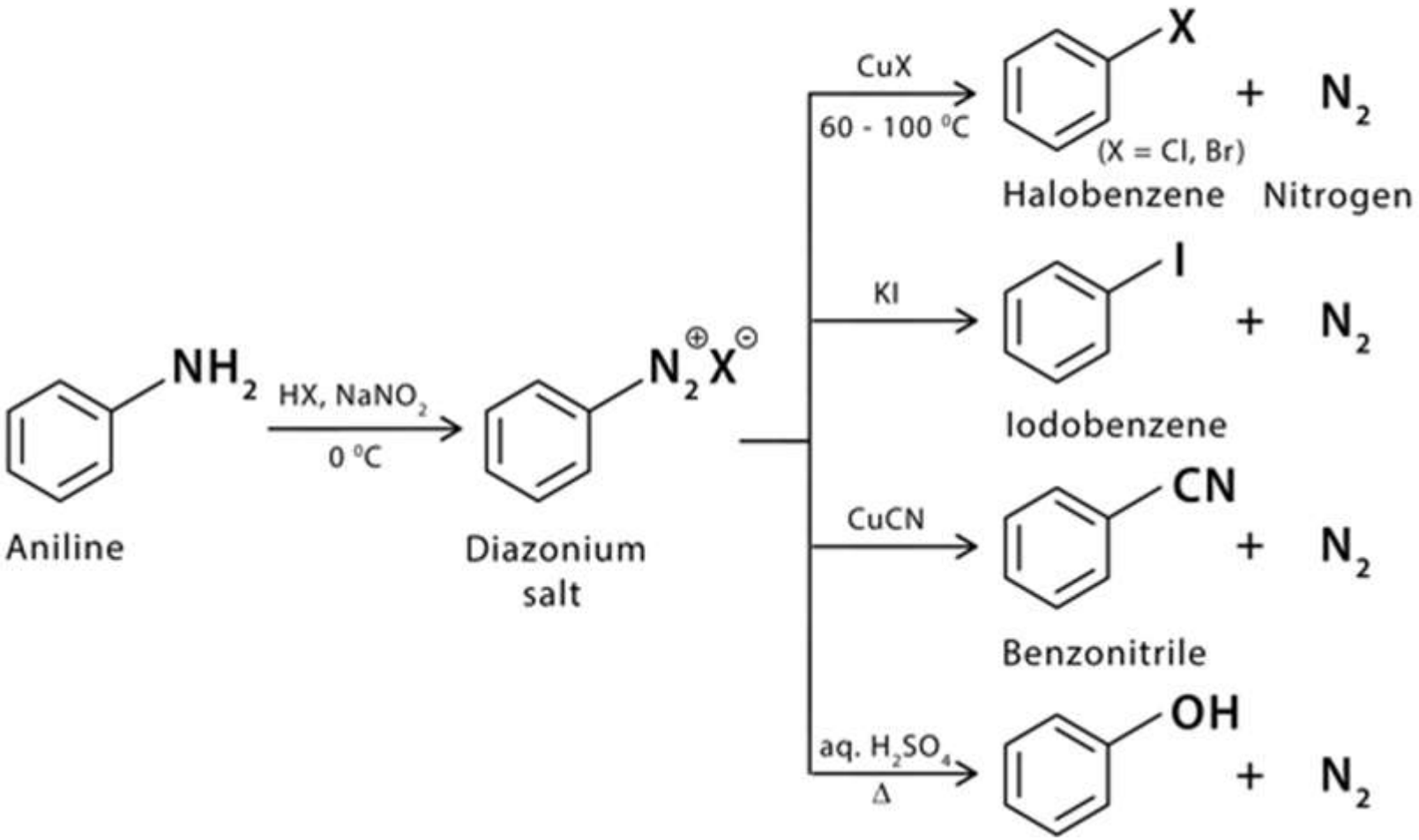
- **In this experiment a separately prepared diazonium salt is combined with copper(I) chloride at 0°C, and then heated to drive the reaction to completeness. Nitrogen gas bubbles off and the diazonium group is replaced with chlorine atom to give the target compound.**
- **The final product is purified by sublimation.**

Reaction Mechanism



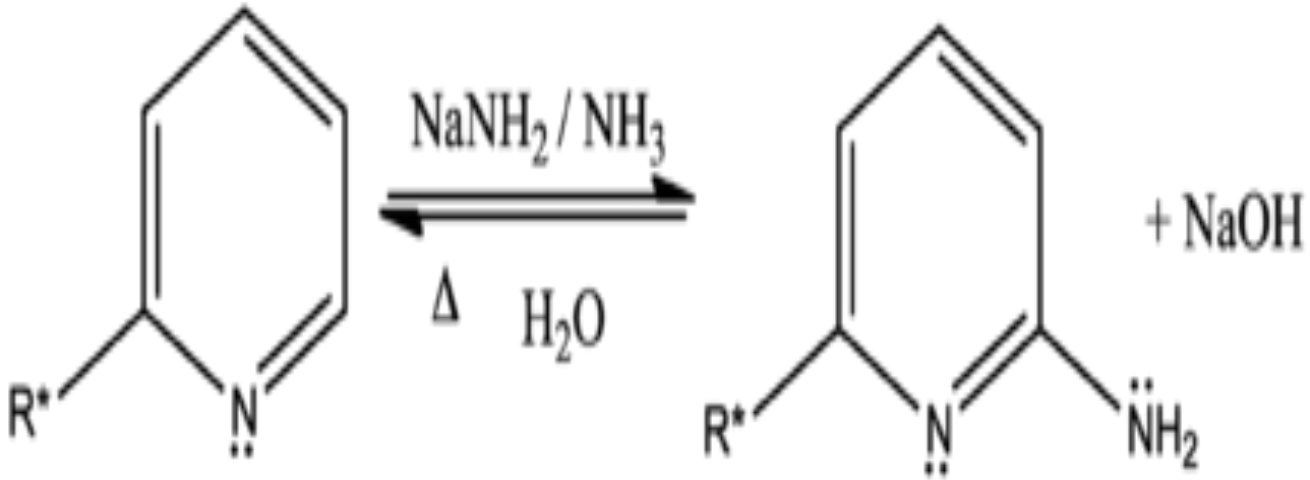
- **The mechanism involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it and resulting in the final product.**

Examples of Sandmeyer Reaction

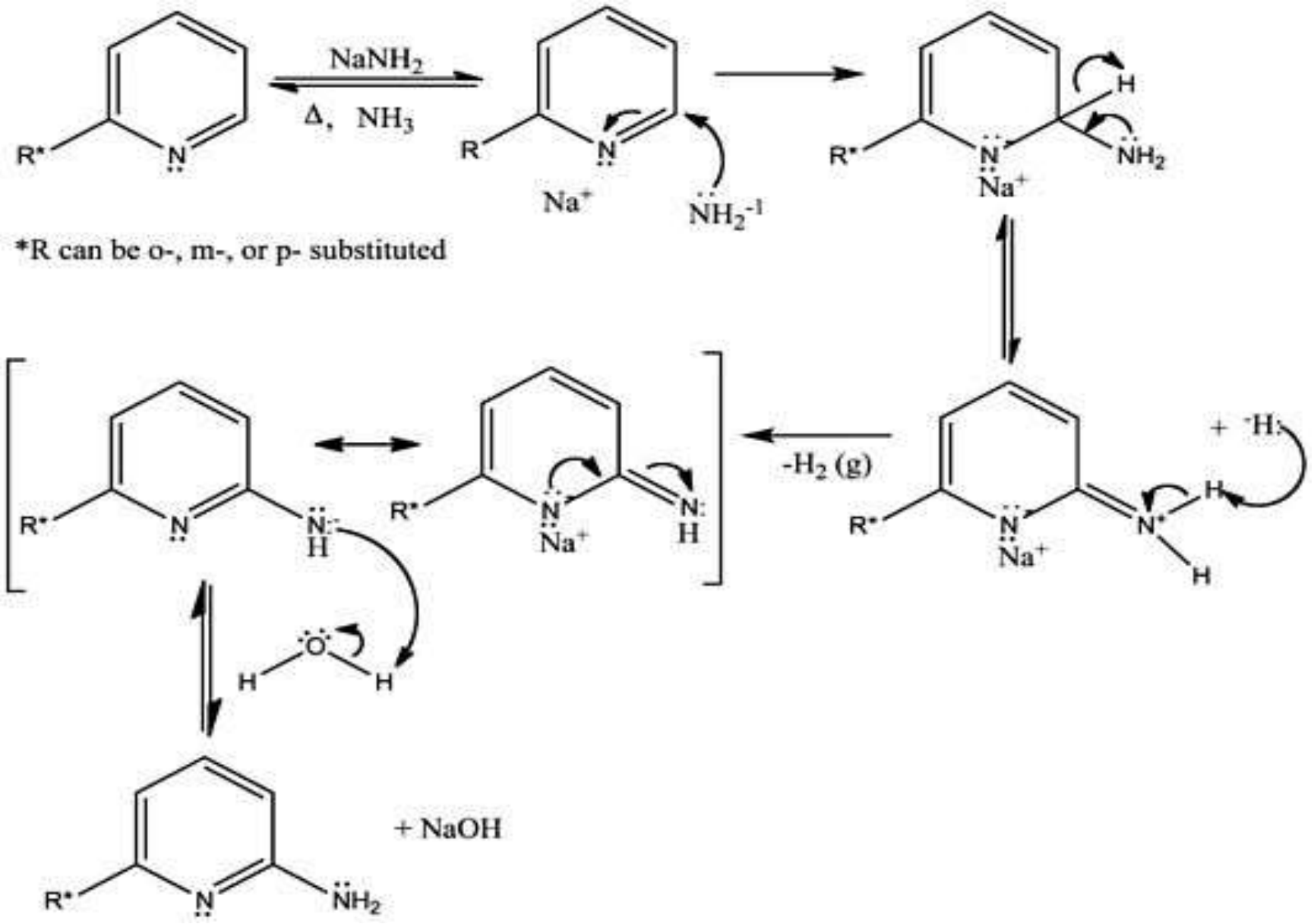


Chichibabin reaction

- The **Chichibabin reaction** (pronounced ' (chē')-chē-bā-bēn) is a method for producing 2-aminopyridine derivatives by the reaction of pyridine with sodium amide. It was reported by Aleksei Chichibabin in 1914.[1] The following is the overall form of the general reaction:

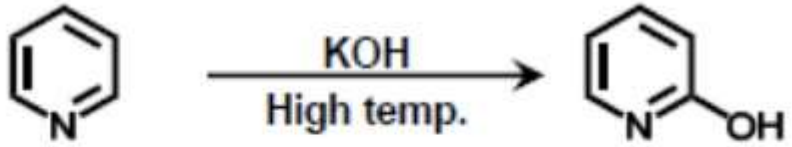

NaNH2 / NH3
Δ
H2O
R*
N
+ NaOH
R*
N
NH2

- The direct amination of pyridine with sodium amide takes place in liquid ammonia. Following the addition elimination mechanism first a nucleophilic NH_2^- is added while a hydride (H^-) is leaving.
- Ciganek describes an example of an intramolecular Chichibabin reaction in which a nitrile group on a fused ring is the source of nitrogen in amination.

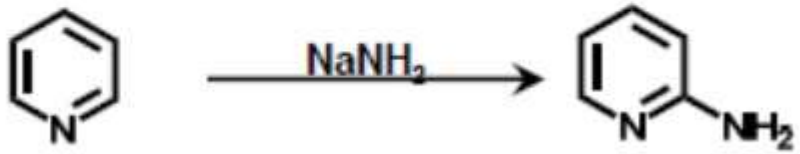


*R can be o-, m-, or p- substituted

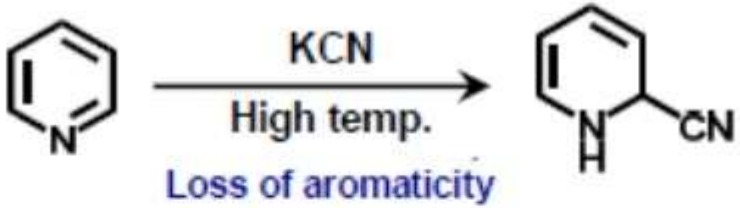
Hydroxylation:



Amination:

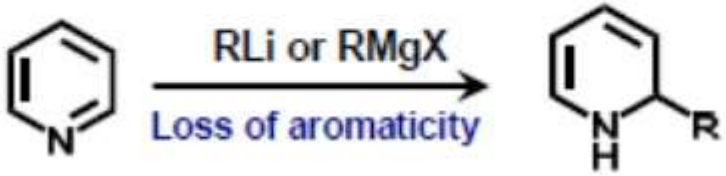


Cyanation:



Loss of aromaticity

Alkylation:



Loss of aromaticity

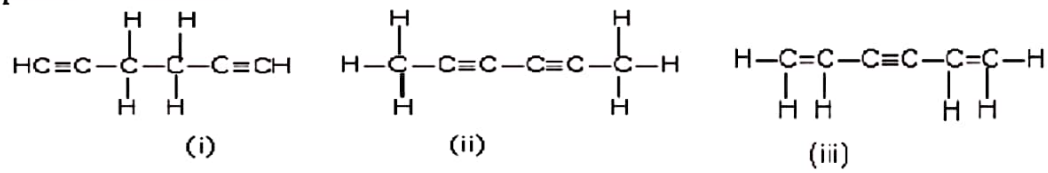
Aromaticity and Electrophilic Aromatic Substitution: Benzene, aromaticity, and other aromatic systems, Nomenclature of benzene derivatives, Other aromatic systems Electron donating and withdrawing groups, Inductive vs. resonance effects; effects of substituents, General mechanism of electrophilic aromatic substitution, Halogenation, Nitration, Sulfonation, Friedel-Crafts Alkylation and Acylation, Directing and activating effects in electrophilic aromatic substitution, Use of electrophilic aromatic substitution in synthesis, Nucleophilic substitution of aryl halides (benzyne and addition-elimination mechanisms).

➢ Structure of Benzene

The molecular formula of benzene has been found from analytical data, to be C_6H_6. Relatively higher proportion of carbon and addition of chlorine to benzene molecule indicate it to be an unsaturated compound. Depending on the various facts available to scientists from time to time, many structures for benzene had been proposed. Some are described below.

❖ Open Chain Structure

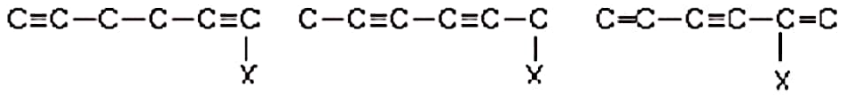
- Based upon observable facts given above and the tetravalency of carbon, the following open chain structures were proposed for benzene.



(i) (ii) (iii)

❖ Drawbacks of open chain structure: The open chain structure for benzene was rejected due to the following reasons:

- Addition reactions usually given by alkenes and alkynes are not given by benzene.
- Benzene forms only one kind of mono-substituted product.
- An open chain structure however, can form more than one kind of monosubstituted product as shown below:



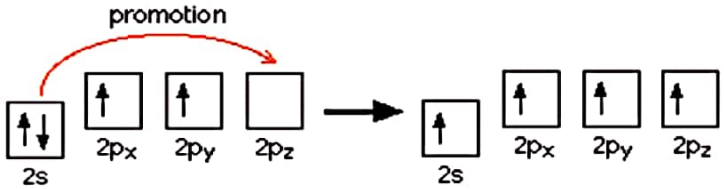
- The open chain compounds do, not give reactions such as FriedelCraft reaction, nitration, sulphonation.
- On reduction with hydrogen in the presence of Ni at 200°C, actually a cyclic compound cyclohexane is obtained.

❖ An orbital model for the benzene structure

✓ ***Building the orbital model***

- Benzene is built from hydrogen atoms ($1s^1$) and carbon atoms ($1s^2 2s^2 2p_x^1 2p_y^1$).
- Each carbon atom has to join to three other atoms (one hydrogen and two carbons) and doesn't have enough unpaired electrons to form the required number of bonds, so it needs to promote one of the $2s^2$ pair into the empty **2pz** orbital.

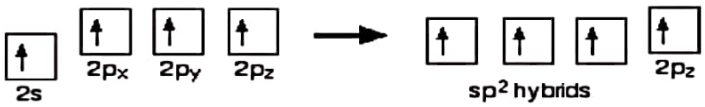
✓ ***Promotion of an electron***



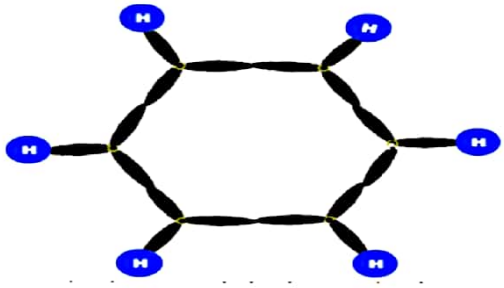
- There is only a small energy gap between the **2s** and **2p** orbitals, and an electron is promoted from the **2s** to the empty **2p** to give 4 unpaired electrons. The extra energy released when these electrons are used for bonding more than compensates for the initial input. The carbon atom is now said to be in an excited state.

✓ ***Hybridisation***

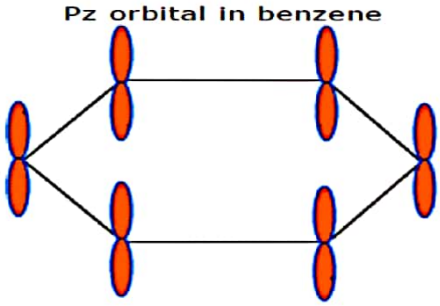
Because each carbon is only joining to three other atoms, when the carbon atoms hybridise their outer orbitals before forming bonds, they only need to hybridise *three* of the orbitals rather than all four. They use the **2s** electron and two of the 2p electrons, but leave the other **2p** electron unchanged.



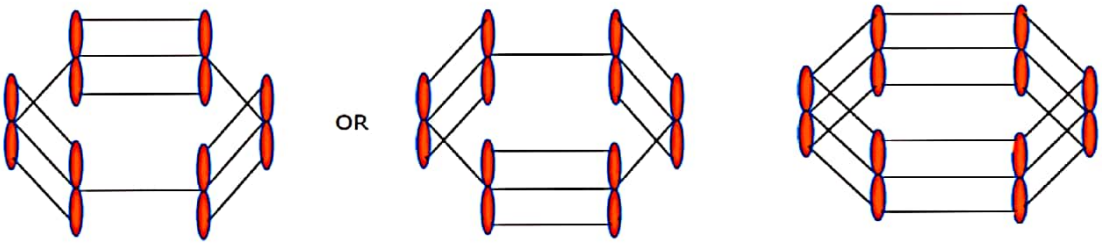
- The new orbitals formed are called **sp^2** *hybrids*, because they are made by an **s** orbital and two **p** orbitals reorganizing themselves.
- The three **sp^2** hybrid orbitals arrange themselves as far apart as possible which is at 120° to each other in a plane. The remaining **p** orbital is at right angles to them.
- Each carbon atom now looks like the diagram on the right. This is all exactly the same as happens in ethene.
- The difference in benzene is that each carbon atom is joined to two other similar carbon atoms instead of just one. Each carbon atom uses the **sp^2** hybrids to form sigma bonds with two other carbons and one hydrogen atom.
- The next diagram shows the sigma bonds formed, but for the moment leaves the **p** orbitals alone.



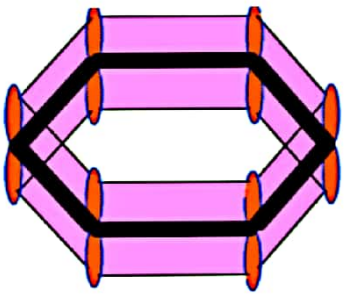
*Since sigma bond results from the overlap of above said planar orbital, all **H** and **C** atoms are in the same plane and their generate a hexagonal ring of **C** atoms.*



*Each **C** atom in benzene also has an unhybrid **2pz** orbital containing one electron. These **2pz** orbital are perpendicular to the plane of sigma bonds.*



*Actually these **2pz** orbital produce a **π (pi)** molecular orbital containing six electrons. One half of this **π (pi)** molecular orbital lies above the plane of hexagonal ring and remaining half below the ring like a sandwich.*



*The overlap of these **2pz** orbital results in the formation of a fully delocalized **π (pi)** bond, which extends all over the six **C** atoms of benzene nucleus. The molecular orbital approach clearly indicates that these six electrons could be found anywhere in highly delocalized manner. As a result of delocalization, a stronger **π (pi)** bond and a more stable benzene molecule is obtained which undergo substitution reactions more frequently than addition reactions.*

❖ **Bond Length Analysis in Benzene**

C-C length in alkane = 1.54°A

C=C length in alkene = 1.34°A

But in benzene,

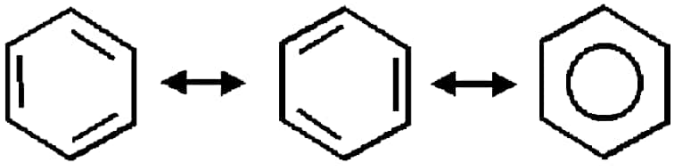
C-C length = 1.397°A

C=C length = 1.397°A

- This shows that in benzene single and double bonds have quite extraordinary character as they do not resemble to alkane and alkene in bond lengths.
- That is why benzene shows a behavior of saturated as well as an unsaturated hydrocarbon simultaneously.

❖ **Modern Representation of Benzene**

- With the help of molecular orbital behavior we conclude that benzene has
  - ✓ A regular hexagonal structure with an inscribed circle.
  - ✓ A hexagon with alternate double and single bonds.



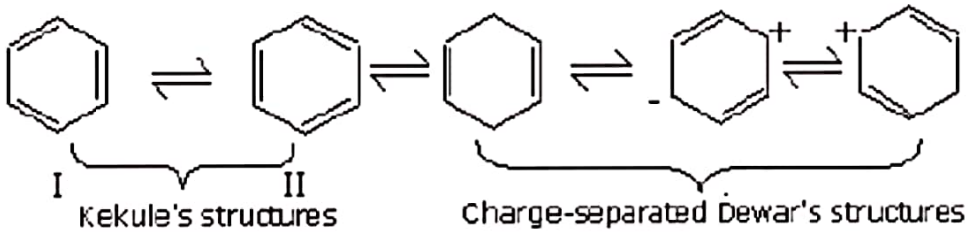
QUESTION: WRITE A NOTE ON THE STABILITY OF BENZENE RING.

ANSWER:

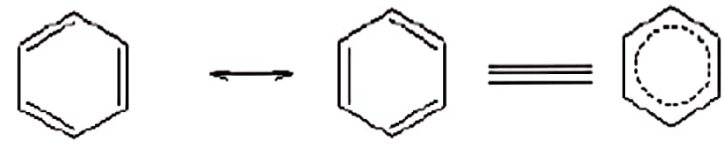
- In benzene ring ***π (pi)*** molecular orbital is in a state of vibration due to this vibration resonance is produced. The stability of benzene ring is due to resonance energy of the system. The resonance energy is the difference in energy content of benzene compared with that of a formal written structure. The Kekule's structure requires localization of **2p**-electrons as specific ***π (pi)*** bonds alternately between particular **C** atoms.
- The actual resonance hybrid structure has these electrons delocalized spread over the whole ring. Hence, ***π (pi)*** electrons of benzene are not readily available at particular positions as in alkenes, and so do not assist the attack of a weak electrophile in the same way as in alkenes. On the other hand the reactivity of benzene ring is also affected by the presence of annular ***π (pi)*** electronic cloud which acts as a repelling shield to any nucleophilic attack. Thus electrophilic substitution is more common in benzene but for a powerful electrophile reagent.

❖ Resonance hybrid structure of benzene

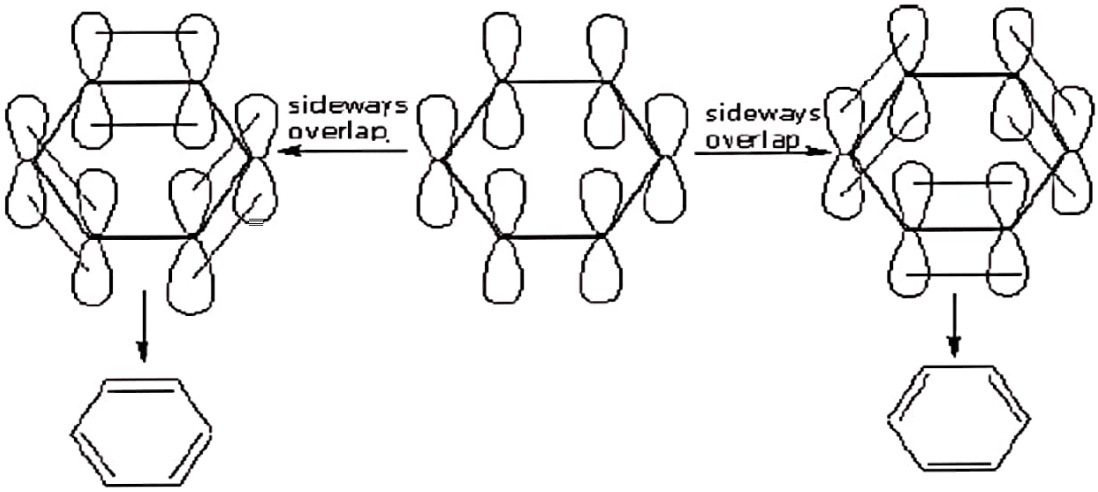
✓ The currently accepted structure was developed by the application of the theory of resonance proposed in 1933. This theory states that benzene is a resonance hybrid of the following canonical forms.



✓ Since, the forms I and II are the most contributing, hence benzene is represented as a hybrid structure of these two structures, i.e.,



Resonance hybrid

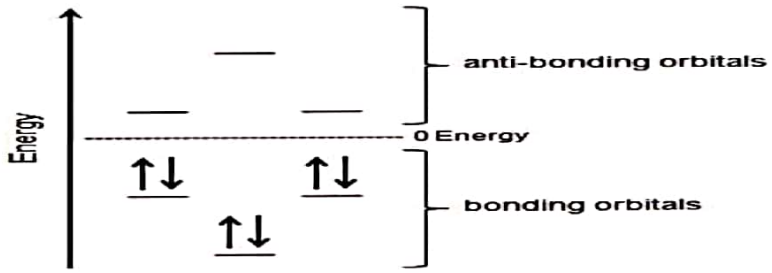


SIR ERICH ARMAND ARTHUR JOSEPH HUCKEL (August 9, 1896, Berlin – February 16, 1980, Marburg) was a German physicist and physical chemist. He is known for two major contributions:

i. The Debye–Huckel theory of electrolytic solutions
ii. The Huckel method of approximate molecular orbital (MO) calculations on π electron systems.

➢ HUCKEL'S RULE

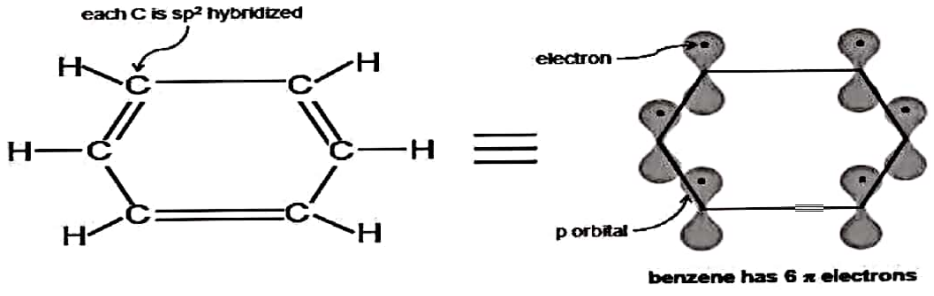
- In 1931, *Sir Erich Huckel* proposed a rule to determine if a planar ring molecule would have aromatic properties. This rule states that if a cyclic, planar molecule has **4n+2 *π-electrons***, it is aromatic. This rule would come to be known as **Huckel's Rule**.
- ***Four Criteria for Aromaticity***
  i. The molecule is cyclic (a ring of atoms)
  ii. The molecule is planar (all atoms in the molecule lie in the same plane)
  iii. The molecule is fully conjugated (p orbitals at every atom in the ring)
  iv. The molecule has 4n+2 *π-electrons* (n=0 or any positive integer)
- **Why 4n+2 *π-Electrons*?**
  - According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons.
  - This is true of aromatic compounds, meaning they are quite stable.
  - With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by **π**), leaving all bonding orbitals filled and no anti-bonding orbitals occupied.
  - This gives a total of **4n+2** *π-electrons*.
  - The molecular orbital diagram for the aromatic compound, benzene, below.



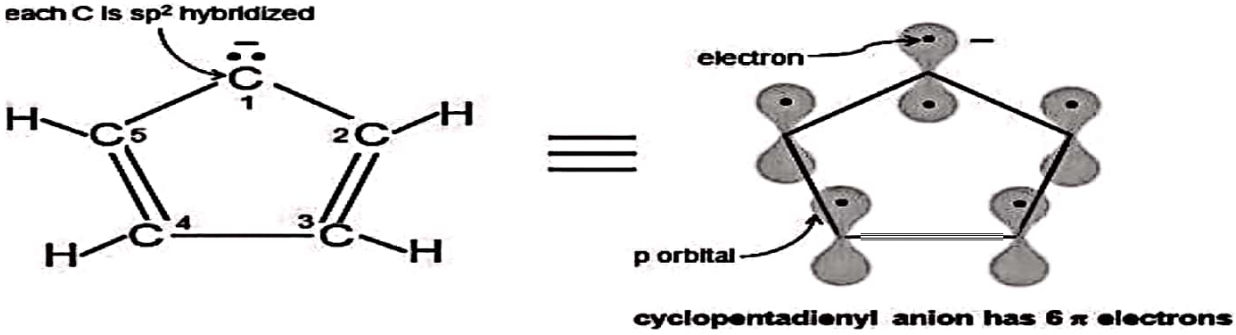
Molecular Orbitals levels of Benzene

  - Benzene has ***6π- electrons***. Its first 2π-electrons fill the lowest energy orbital, and it has ***4π-electrons*** remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.
- **Which Electrons are π -Electrons**
  - **Huckel's Rule** is figuring out which electrons in the compound are actually **π-electrons**.
  - The rule is quite straight forward; **π-electrons** lie in **p orbitals**.
  - **Sp^2 hybridized** atoms have **1 p orbital** each.
  - So if every molecule in the cyclic compound is **sp^2 hybridized**, this means the molecule is fully conjugated (has **1 p orbital** at each atom), and the electrons in these **p orbitals** are the **π-electrons**.
  - A simple way to know if an atom is **sp^2 hybridized** is to see if it has 3 attached atoms and no lone pairs of electrons.
  - In a cyclic hydrocarbon compound with alternating single and double bonds, each carbon is attached to **1 hydrogen** and **2 other carbons**. Therefore, each carbon is **sp2 hybridized** and has a p orbital.
  - As for example, benzene:

Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.

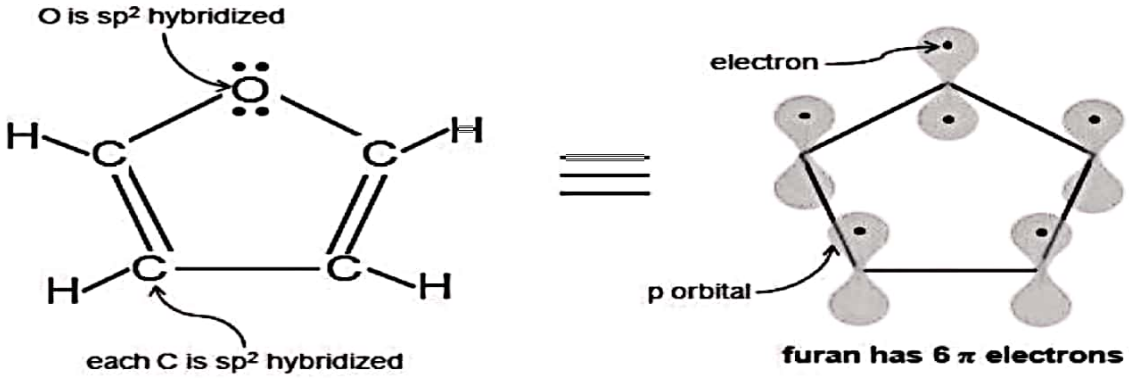


- **Aromatic Ions**
  - Hückel's Rule also applies to ions. As long as a compound has 4n+2 π electrons, it does not matter if the molecule is neutral or has a charge.
  - ***For example, cyclopentadienyl anion is an aromatic ion***: **Carbons 2-5** are **sp2 hybridized** because they have 3 attached atoms and have no lone electron pairs. Whereas about **carbon-1** another simple rule to determine if an atom is **sp2 hybridized** is if an atom has 1 or more lone pairs and is attached to an sp2 hybridized atom, then that atom is **sp2 hybridized** also. Therefore, carbon 1 has a **p orbital**. ***Cyclopentadienyl anion*** has **6 π electrons** and fulfills the **4n+2 rule**.



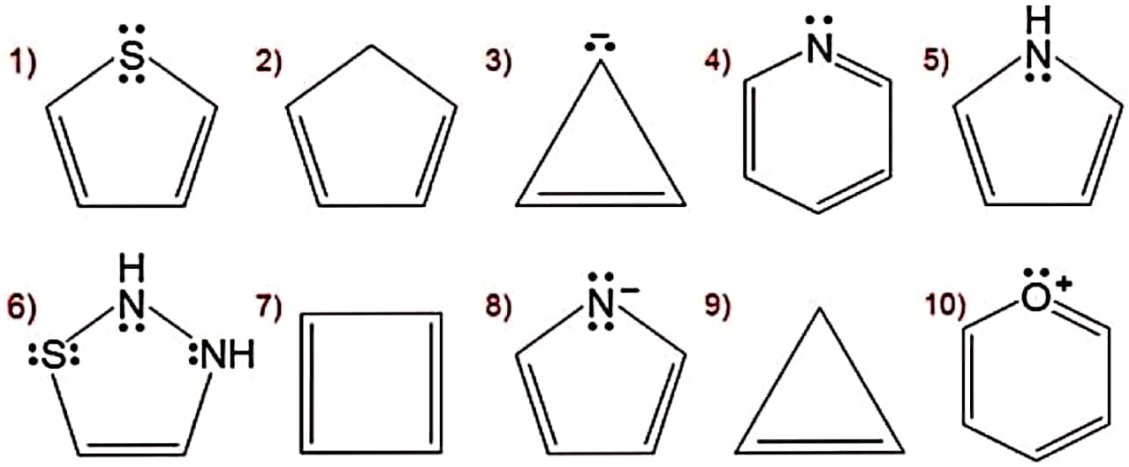
cyclopentadienyl anion has 6 π electrons

- **Heterocyclic Aromatic Compounds**
  - Compounds with elements other than carbon in the ring can also be aromatic, as long as they fulfill the criteria for aromaticity. These molecules are called heterocyclic compounds because they contain 1 or more different atoms other than carbon in the ring.
  - **A common example in furan:** This contains an oxygen atom. All carbons in furan are **sp2 hybridized**. The oxygen has at least 1 lone electron pair and is attached to an **sp2 hybridized** atom, so it is **sp2 hybridized** as well. Notice how oxygen has 2 lone pairs of electrons. An **sp2 hybridized** atom only has **1 p orbital**, which can only hold **2 electrons**, while the other pair is in an **sp2 orbital**. So, only 1 of oxygen's **2 lone electron pairs** are **π electrons**. Furan has **6 π electrons** and fulfills the **4n+2** rule.



furan has 6 π electrons

QUESTION: Using the criteria for aromaticity, determine if the following molecules are aromatic.



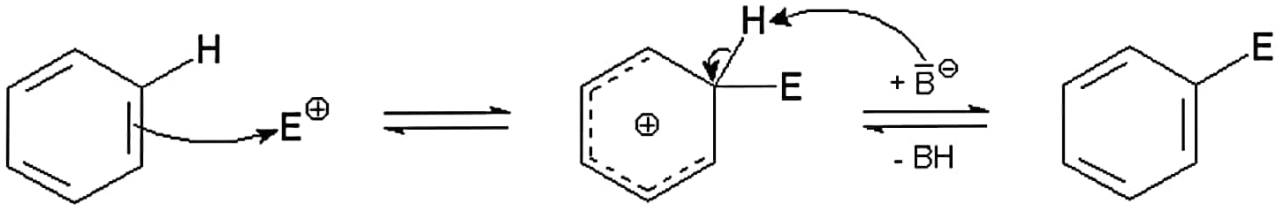
ANSWER:

1. **Aromatic** - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1
2. **Not aromatic** - not fully conjugated, top C is sp^3 hybridized
3. **Not aromatic** - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2
4. **Aromatic** - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1
5. **Aromatic** - there are 6 π electrons, n=1
6. **Not aromatic** - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5
7. **Not aromatic** - there are 4 π electrons, n=1/2
8. **Aromatic** - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1
9. **Not aromatic** - not fully conjugated, top C is sp^3 hybridized
10. **Aromatic** - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

❖ THE ELECTROPHILIC SUBSTITUTION REACTION BETWEEN BENZENE

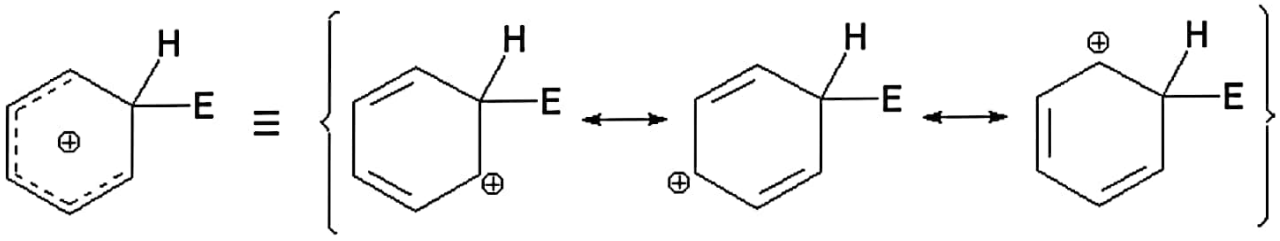
➢ Mechanism of Electrophilic Aromatic Substitution (Ar-SE)

- Electrophilic aromatic substitution is a multistep process.
- In the first step, the addition of an electrophile yields a high-energy carbocation in which the aromatic **π system** has been broken. Subsequently, the aromatic system is recovered by splitting off a proton. Therefore, the mechanism of an **electrophilic aromatic substitution** (**Ar-SE**) may be classified as an ***addition-elimination mechanism***.

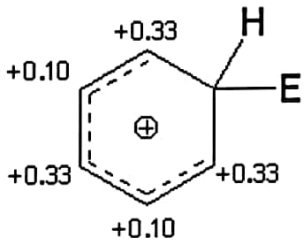


σ complex

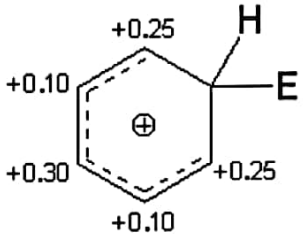
- Initially, the approaching electrophile interacts with the nucleophilic, **aromatic π electron cloud**. The so-called **π complex**.
- The **π complex** that is initially generated by the **aromatic π system's** nucleophilic attack on the electrophile is then rapidly converted into a **cyclohexadienyl cation** known as either the **Wheland complex** or **the σ complex**, or **the arenium ion**. In the **σ complex**, the electrophile is connected to one of the aromatic ring carbons by a **σ bond**.
- *In the second step*, a proton is eliminated from the **σ complex** and then accepted by a base. The base is frequently the counterion of the electrophile; occasionally, the solvent acts as the base. The first step of **Ar-SE** reaction, that is, the formation of the **σ complex**, requires a particularly high amount of energy, as the aromatic π system is broken. In the second step, that is, in the deprotonation, the **aromatic π system** is recovered.
- *In some cases*, it is not a proton but another cation that is eliminated from the **σ complex**. As a result, the aromatic compound is defunctionalized - it loses a functional group. Such a reaction is called an ***Ipso Attack***.
- In the **cyclohexadienyl cation** (**σ complex**), the **positive charge** is delocalized - that is, it is shared by several carbon atoms.



- If the three resonance structures of the **σ complex** are simply superposed, the positive charge in each ***ortho*** and ***para*** position would amount to **+0.33**. In an improved model, the ***meta*** position also carries a small positive charge (+0.10).

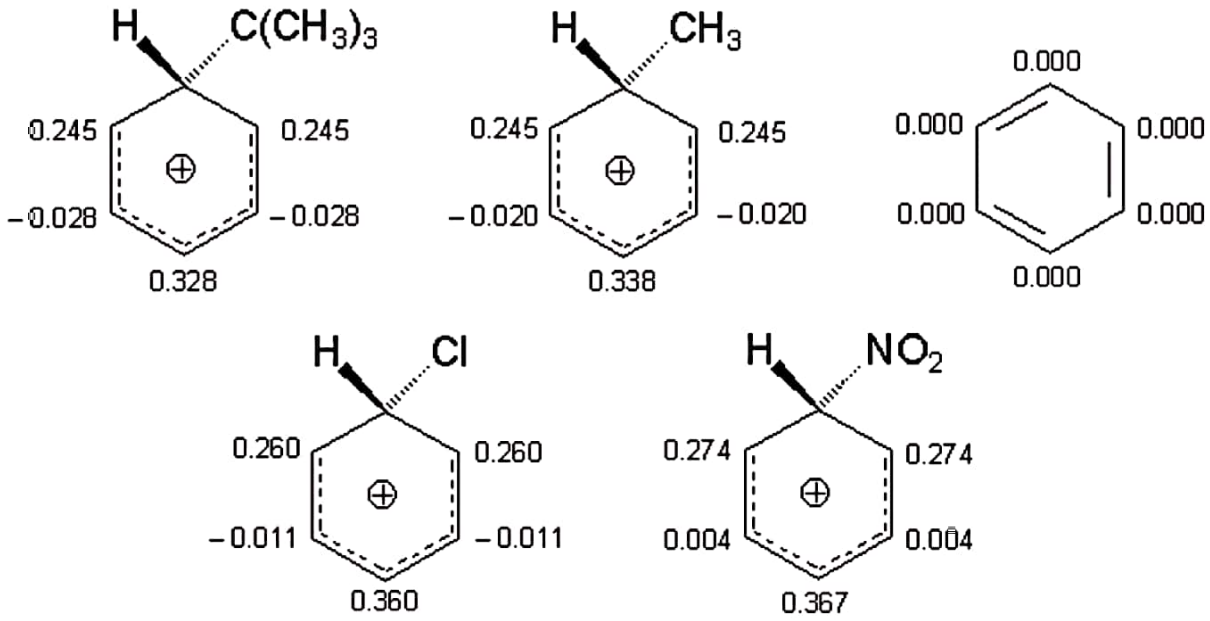


simple model



improved model

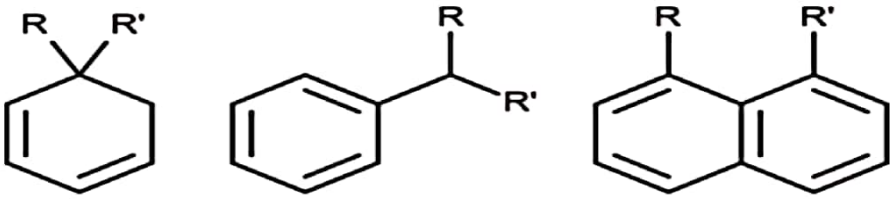
- Atom's electric charges of several σ complexes



QUESTION: WHAT ARE *IPSO*, *MESO*, AND *PERI* SUBSTITUTIONS IN ORGANIC CHEMISTRY?

ANSWER:

- ***Ipso Substitution:*** The *ipso-* prefix is used when two substituents share the same ring position in an intermediate compound. This could occur in an electrophilic aromatic ring substitution.
- ***Meso Substitution:*** The *meso-* prefix is used when substituents occupy a benzylic position, when the first carbon covalently bonds adjacent to benzene or other aromatic ring. It is seen in acridines and calixarenes.
- ***Peri Substitution:*** The *peri-* prefix is used to describe substituents at the 1 and 8 positions. It is seen specifically in naphthalenes.



❖ SUBSTITUTION REACTIONS OF BENZENE DERIVATIVES

- According to the considerations above, substituents may be classified into two main groups:
  i. ACTIVATING SUBSTITUENTS: Those are capable of stabilizing the positive charge of the **σ complex**. Compared to benzene, such substituents result in a higher reaction rate of (a second) electrophilic aromatic substitution.
  Examples of activating groups in the relative order from the most activating group to the least activating:

  $-NH_2$, $-NR_2$ > -OH, -OR> -NHCOR> $-CH_3$ and other alkyl groups

  [**R** as alkyl groups (C_nH2_{n+1})]

  ii. DEACTIVATING SUBSTITUENTS: Those additionally destabilize the positive charge of the **σ complex**. Compared to benzene, such substituents characteristically result in a lower reaction rate of (a second) electrophilic aromatic substitution.
  Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

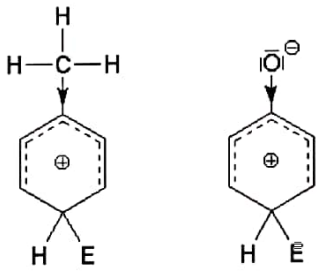
  $-NO_2$, $-CF_3$> -COR, -CN, $-CO_2R$, $-SO_3H$ > Halogens

  [**R** as alkyl groups (C_nH_{2n+1})]

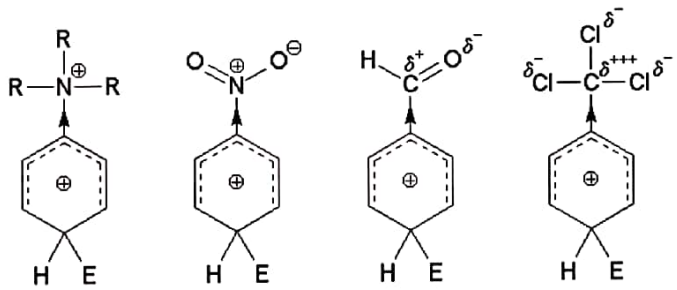
  The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is: **F> Cl > Br > I**

- Halogen substituents are a little unusual in that they are deactivating but still direct **ortho/ para**. The reason is that they are both inductive electron withdrawing (electronegativity) and resonance donating (lone pair donation). The inductive effect lowers the reactivity but the resonance effect controls the regiochemistry due to the stability of the intermediates.

- The stabilization as well as the destabilization of the **σ complex** may be the outcome of two different effects.
  i. Inductive increase or decrease, respectively, in the aromatic system's electron density through polarization of the σ bond between the substituent and the aromatic ring. This quality of substituents is known as the ***electron-donating inductive effect (+I effect)*** *or* ***electron-withdrawing inductive effect (-I effect)****, respectively.*

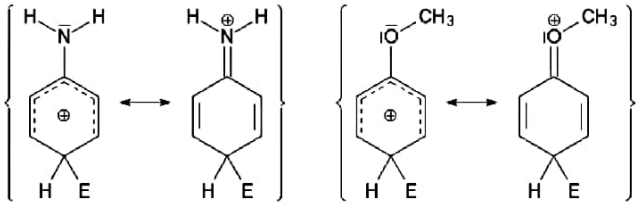


Alkyl groups and the negatively charged oxygen of a phenolate anion are examples of substituents with a **+I effect**

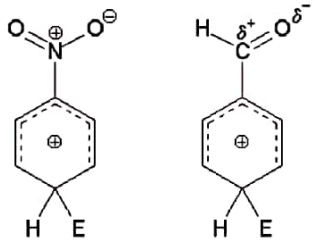


The atom of a substituent with a -I effect that is directly bound to the aromatic ring carbon carries a partially positive charge. R_3N^+- and SO_3H- are examples of substituents with a **-I effect**

ii. *An increase or decrease of the aromatic system's electron density through* ***resonance*** *(****mesomerism****). That is, the substituent participates in the aromatic π electron system either by donating* ***π electron density (lone electron pair)*** *or by accepting* ***π electron density****. These qualities of a substituent are called* ***electron-donating mesomeric effect (+M effect)*** *or* ***electron-withdrawing mesomeric effect (-M effect)****, respectively. In Lewis formulas, the mesomeric effect of a substituent is illustrated by several possible resonance structures of the σ complex. Mesomeric effects are usually much stronger than inductive effects.*

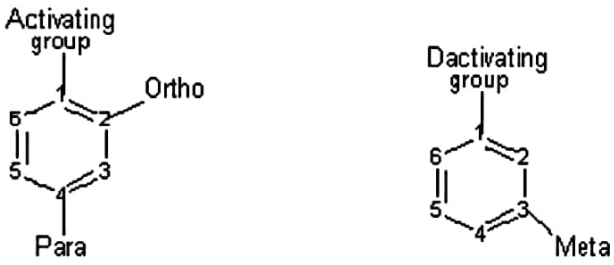


Substituents such as the amino group (NH_2-) of aminobenzene (aniline) or the methoxy group (OCH_3-) of methoxybenzene (anisole) show a considerable **+M effect**.



The nitro group and carboxyl groups are examples of substituents with a **-M effect**.

- The ***activating group*** directs the reaction to the ortho or para position, which means the electrophile substitute the hydrogen that is on **carbon 2** or **carbon 4**.
- The ***deactivating group*** directs the reaction to the meta position, which means the electrophile substitute the hydrogen that is on **carbon 3** with the exception of the halogens that is a deactivating group but directs the ortho or para substitution.

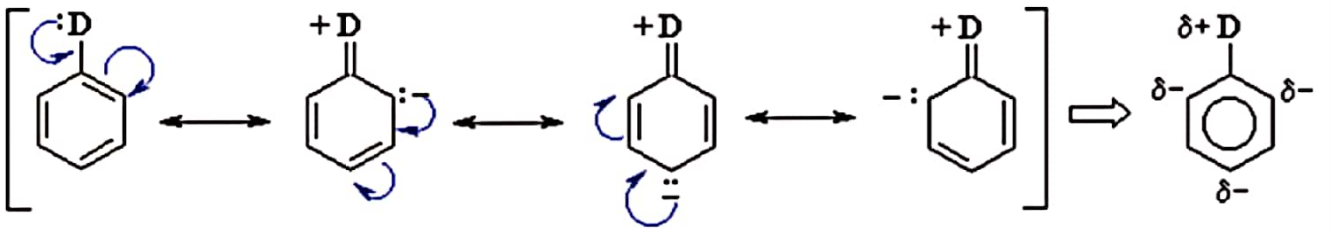


1. ACTIVATING GROUPS *(ortho or para directors)*

- When the substituents like OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effects which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

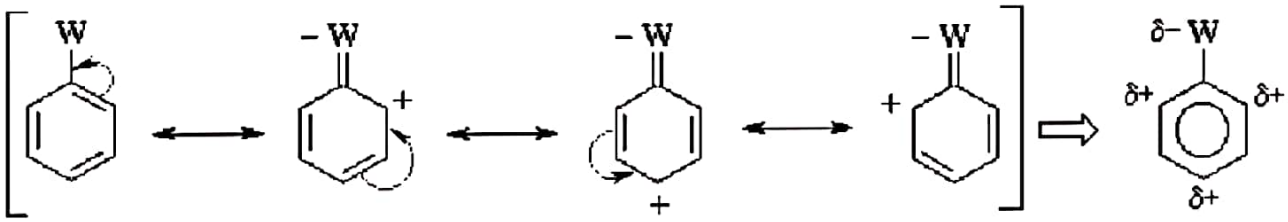
OR

- **Electron Donating Groups** (**EDG**) with lone pairs (*e.g.* :O:Me, **:**NH_2) on the atoms adjacent to the **π** system activate the aromatic ring by increasing the electron density on the ring through a resonance donating effect. The resonance only allows electron density to be positioned at the **ortho** and **para** positions. Hence these sites are more nucleophilic, and the system tends to react with electrophiles at the **ortho** and **para** sites.



2. DEACTIVATING GROUP *(meta directors)*

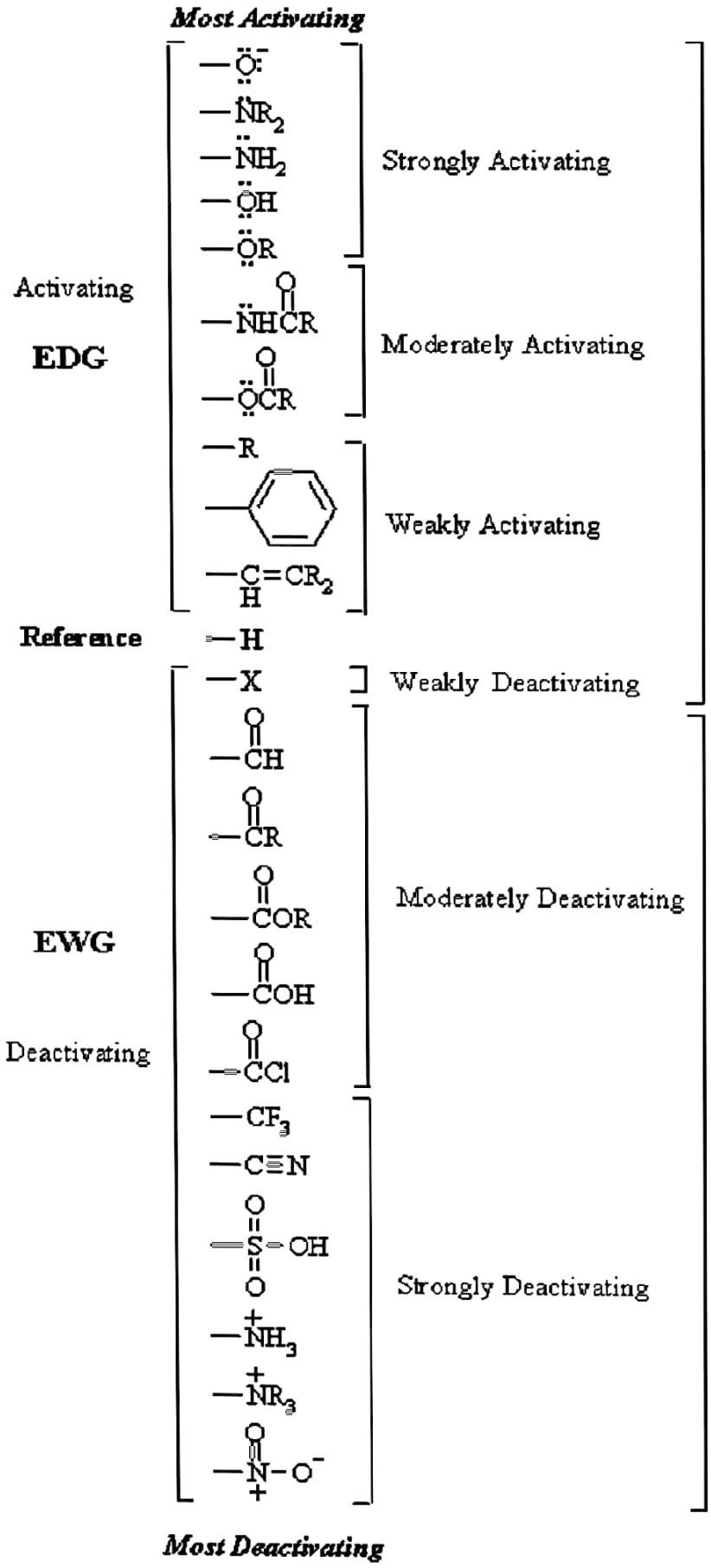
- The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws the electrons away from the ring.
- **Electron Withdrawing Groups** (**EWG**) with π bonds to electronegative atoms (e.g. C=O, NO_2) adjacent to the **π system** deactivate the aromatic ring by decreasing the electron density on the ring through a resonance withdrawing effect. The resonance only decreases the electron density at the ortho and para positions. Hence these sites are less nucleophilic, and so the system tends to react with electrophiles at the **Meta** sites.



✓ ***There are two main electronic effects that substituents can exert:***

- **RESONANCE** effects are those that occur through the π system and can be represented by resonance structures. These can be either electron donating (e.g. **OMe**) where π electrons are pushed toward the arene or electron withdrawing (e.g. **C=O**) where **π electrons** are drawn away from the **arene**.
- **INDUCTIVE** effects are those that occur through the π system due to electronegativity type effects. These too can be either electron donating (e.g. **Me**) where π electrons are pushed toward the arene or electron withdrawing (e.g. **CF_3**, **+NR_3**) where **π electrons** are drawn away from the **arene**.

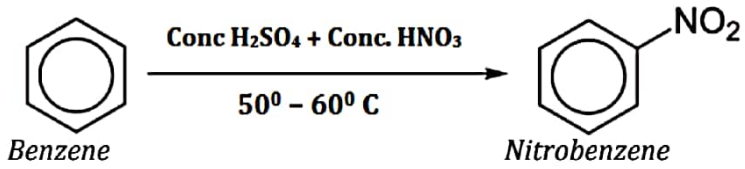
NOTE BY:
WHAT ARE ARENES?
Arenes are aromatic hydrocarbons. The term "aromatic" originally referred to their pleasant smells, but now implies a particular sort of delocalised bonding.
The **arenes** are likely to meet at this level are based on benzene rings. The simplest of them is benzene itself, C_6H_6. The next simplest is methylbenzene (old name: toluene) which has one of the hydrogen atoms attached to the ring replaced by a methyl group - $C_6H_5CH_3$.



EDG / activating groups direct *ortho / para*
EWG / deactivating groups direct *meta*
***except* halogens (X)** which are deactivating but direct *ortho / para*
EDG add electron density to the p system making it more nucleophilic
EWG remove electron density from the p system making it less nucleophilic
EWG = Electron Withdrawing Group
EDG = Electron Donating Group
The **H atom** is the standard and is regarded as having no effect.

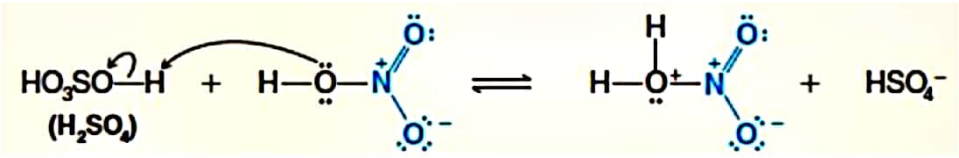
1. NITRATION OF BENZENE

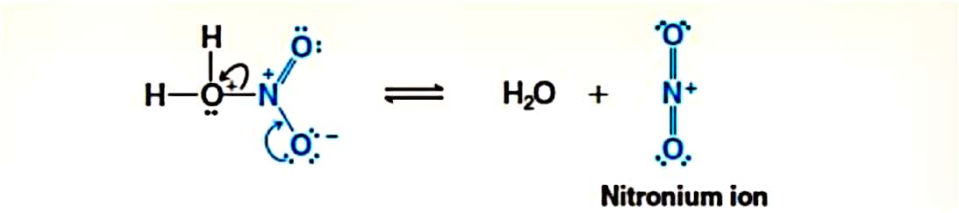
- Benzene reacts with concentrated nitric acid at $50^0 - 60^0$ C in the presence of concentrated sulphuric acid to form nitrobenzene. This reaction is known as nitration of benzene.
- ***Reaction type***: *Electrophilic Aromatic Substitution*
- **General Reaction**



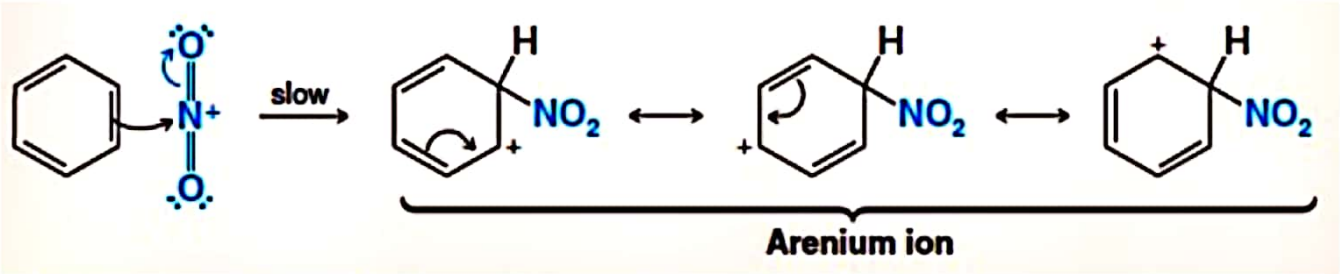
- ***Reaction Mechanism***

Step 1: Nitric acid accepts a proton from sulphuric acid and then dissociates to form **nitronium ion**.

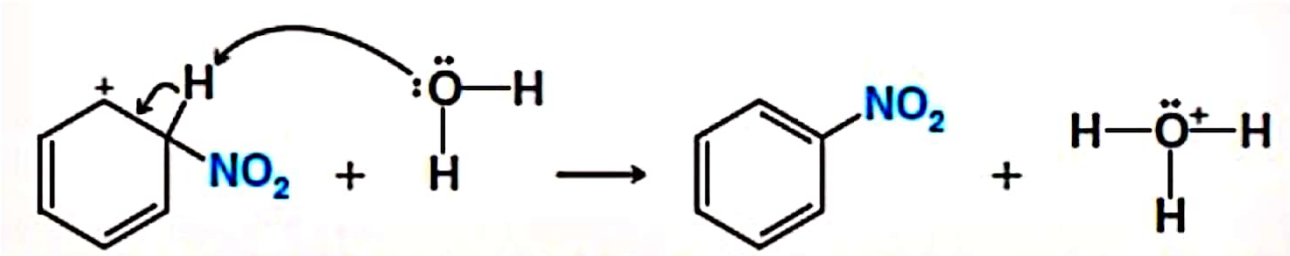




Step 2: The **nitronium ion** acts as an **electrophile** in the process which further reacts with benzene to form **arenium ion.**

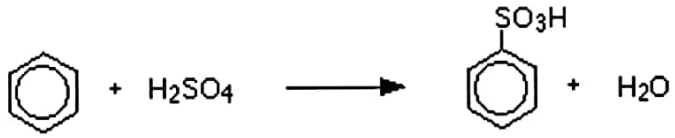


Step 3: The **arenium** ion then loses its proton to Lewis base forming nitrobenzene.



2. SULFONATION OF BENZENE

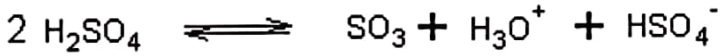
- Sulfonation of benzene is a process of heating benzene with fuming sulphuric acid ($H_2SO_4 + SO_3$) to produce **benzenesulfonic acid**. The reaction is reversible in nature.
- Sulphonation of benzene requires "***fuming sulphuric acid***", which is sulphuric acid with extra SO_3 added. The sulphuric acid produces even more SO_3, which is the electrophile in this reaction.
- **Reaction type:** *Electrophilic Aromatic Substitution*
- **General Reaction**



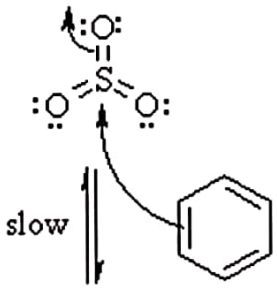
Benzene *Sulphuric Acid* *Benzenesulfonic Acid*

- ***Reaction Mechanism***

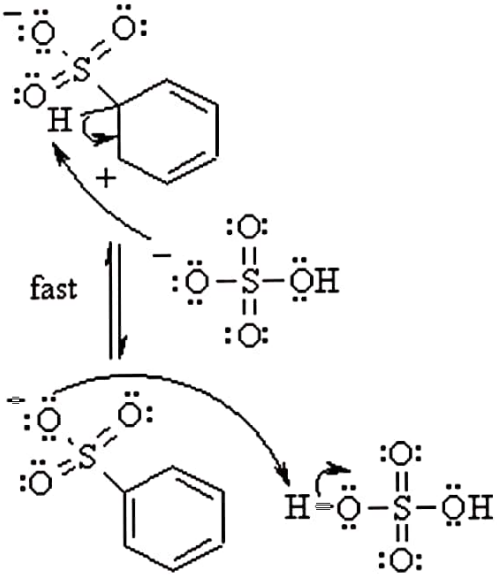
Step I: Formation of Electrophilic species, SO_3 which can be formed by the loss of water from the sulfuric acid



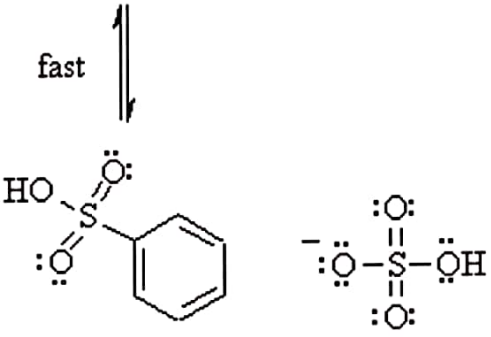
Step 2:
The **π electrons** of the aromatic **C=C** act as a nucleophile, attacking the electrophilic S, pushing charge out onto an electronegative O atom. This destroys the aromaticity giving the **cyclohexadienyl cation** intermediate.



Step 3:
Loss of the proton from the **sp3 C** bearing the **sulfonyl-group** reforms the **C=C** and the aromatic system.

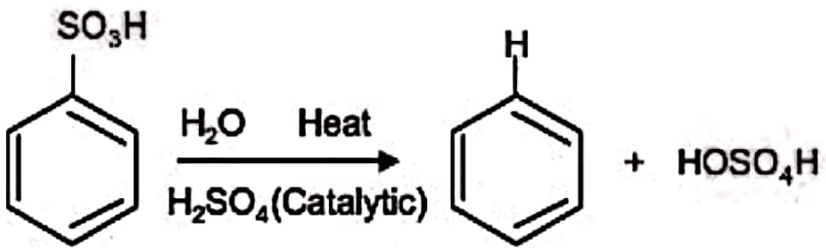


Step 3:
Protonation of the conjugate base of the sulfonic acid by sulfuric acid produces the sulfonic acid.



3. REVERSE SULFONATION

- Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



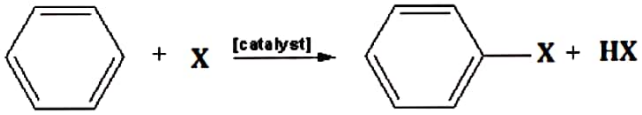
❖ Applications of Nitration and Sulfonation

- **Nitration** is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic nitrations are very important intermediates in industrial chemistry.

- Because **sulfonation** is a **reversible reaction**, it can also be used in further substitution reactions in the form of a directing blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is completed it can be removed by reverse sulfonation. Benzenesulfonic acids are also used in the synthesis of detergents, dyes, and sulfa drugs. Bezenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

4. HALOGENATION OF BENZENE

- **Reaction type:** *Electrophilic Aromatic Substitution*
- An electrophilic aromatic halogenation is a type of electrophilic aromatic substitution. This organic reaction is typical of aromatic compounds and a very useful method for adding substituents to an aromatic system.
- A few types of aromatic compounds, such as phenol, will react without a catalyst, but for typical benzene derivatives with less reactive substrates, a Lewis acid catalyst is required. Typical **Lewis acid catalysts** include **$AlCl_3$, $FeCl_3$, $FeBr_3$,** and **$ZnCl_2$**. These work by forming a highly electrophilic complex which is attacked by the benzene ring.
- ***Electrophilic species***: the halonium ion (i.e. **X^+; X = Cl_2** and **Br_2**) formed by the removal of a halide ion by the Lewis acid catalyst
- Restricted for **I^-** or **F^-** are usually introduced using alternative methods
- **General Reaction:**

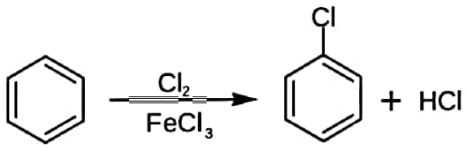


X = Halogen

CATALYSTS = Lewis acid catalysts ($AlCl_3$, $FeCl_3$, $FeBr_3$, and $ZnCl_2$)

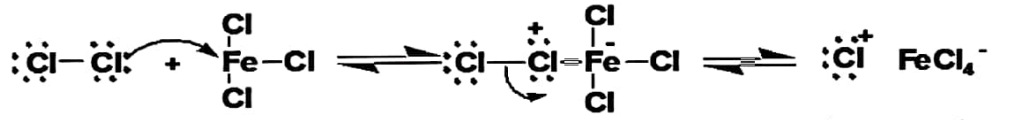
A. Chlorination of Benzene

- **General Reaction:**



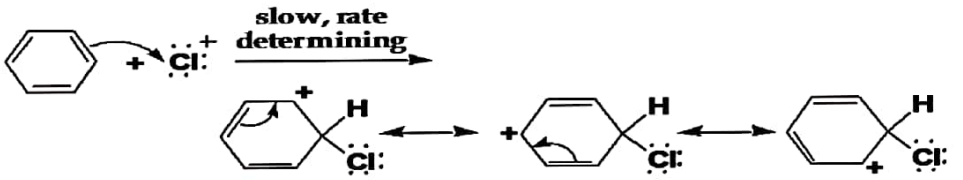
- ***Mechanism of Chlorination of Benzene***

Step 1: *formation of a chloronium ion.*



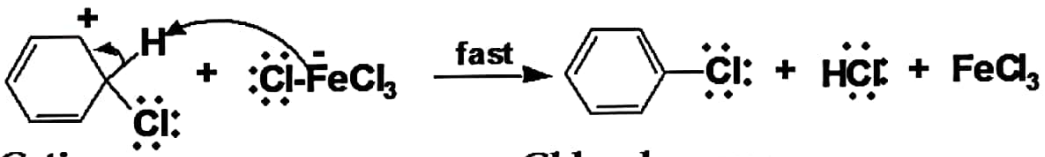
Chlorine (a Lewis base) | **Ferric chloride (a Lewis acid)** | **A molecular complex with a positive charge on chlorine** | **An ion pair containing a chloronium ion**

Step 2: *attack of the chloronium ion on the ring*



Resonance-stabilized cation intermediate; the positive charge is delocalized onto three atoms of the ring

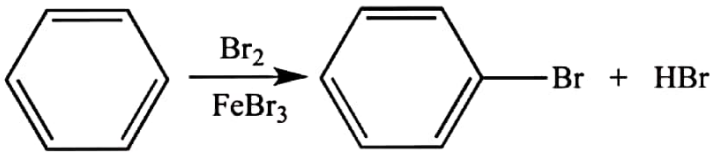
Step 3: *proton transfer regenerates the aromatic character of the ring.*



Cation intermediate | **Chlorobenzene**

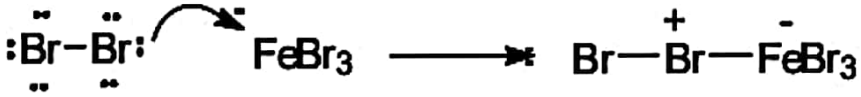
B. Bromination of benzene

- **General Reaction:**



- ***Mechanism of Bromination of benzene***

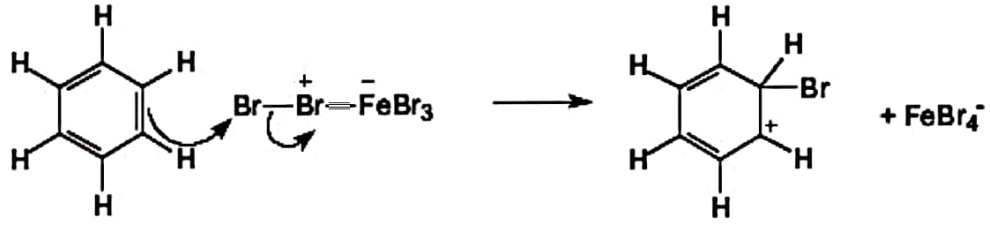
Step 1: Generate of Electrophile



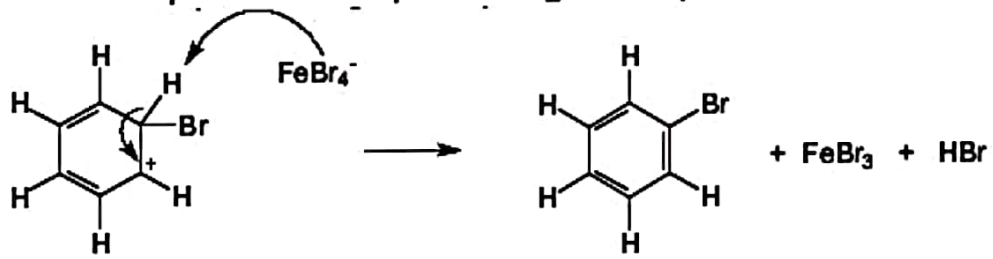
(stronger electrophile than Br_2)

- Before the electrophilic aromatic substitution can take place, the electrophile must be activated.
- A strong Lewis acid catalyst, such as $FeBr_3$, should be used.

Step 2: Electrophilic attack and formation of the sigma complex.



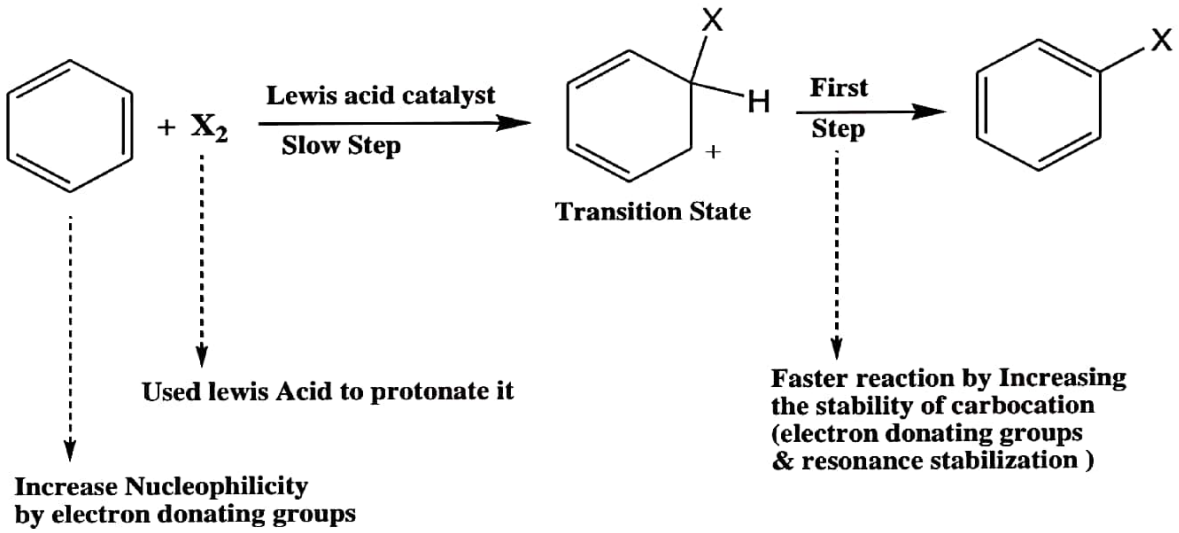
Step 3: Loss of a proton to give the products.



QUESTION: WHY IODINATION AND FLUORINATION OF BENZENE DIFFICULT?

ANSWER:

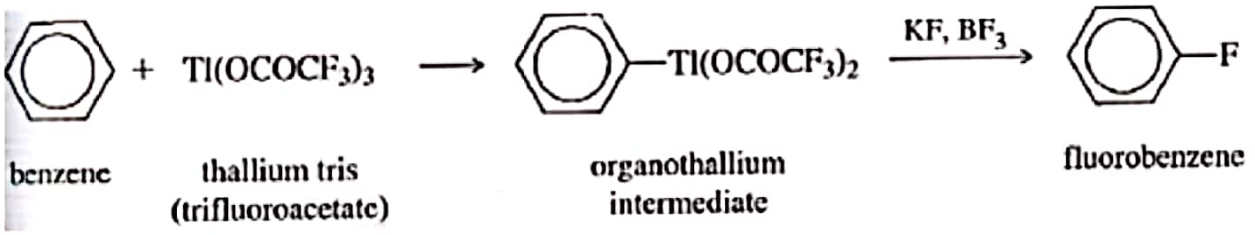
- When Benzene or the halogen in the starting material has to be slightly more reactive than the other.
- For satisfying this condition, electron donating groups attached to the phenyl ring making it more nucleophilic are preferred over unsubstituted Benzene. Also, the electrophilicity of the halogen is increased by using a Lewis acid catalyst thereby making it more reactive.
- These changes in turn help to achieve transition state faster and stabilize it better.
- **Electrophilic aromatic substitution reaction**

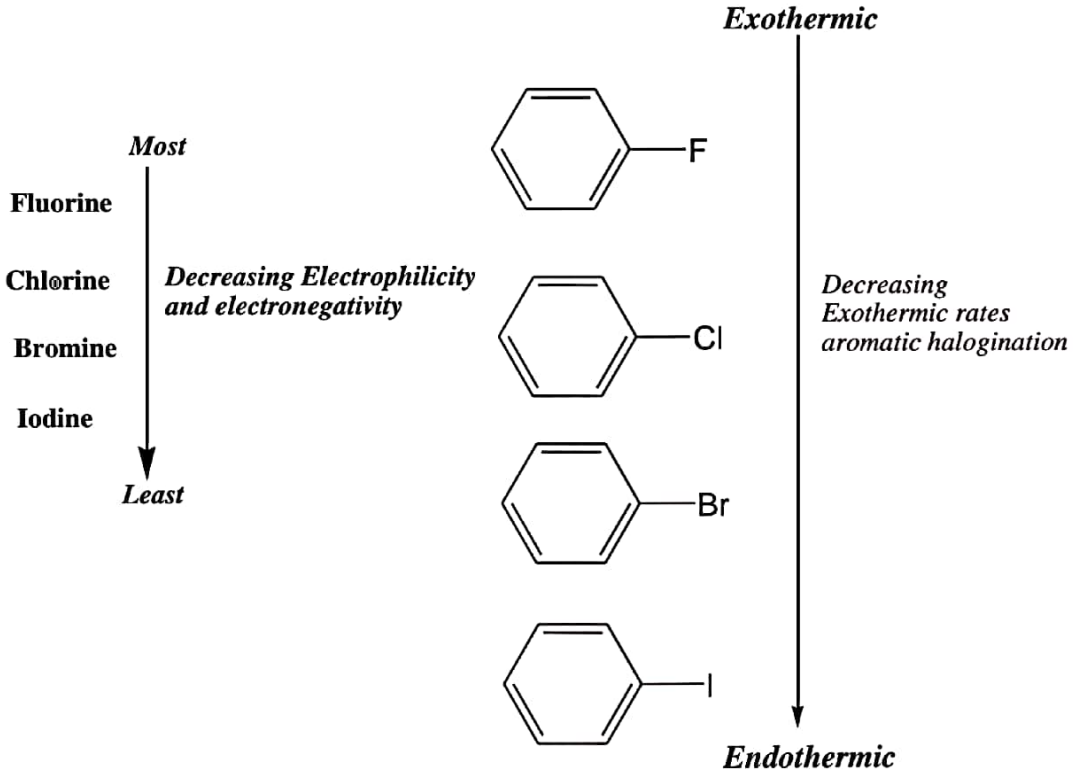


- In case of the halogens, the electronegativity and electrophilicity decrease from **F** to **I** in the periodic table. **Fluorine** is most **electrophilic**, and **Iodine** is least. Therefore, **Fluorination** is highly reactive, and **Iodination** is highly unreactive for electrophilic aromatic substitution reactions.
- The exothermic rates of aromatic halogenation also decrease from **Fluorine** to **Iodine**. Fluorination reaction being highly exothermic and explosive, the reaction cannot be controlled resulting in polyfluorinated products. For Iodination, the reaction is endothermic with 12kJ/mol of energy absorbed. Therefore, it cannot be done using the conventional method using Lewis acid catalyst and requires strong oxidizing agents.

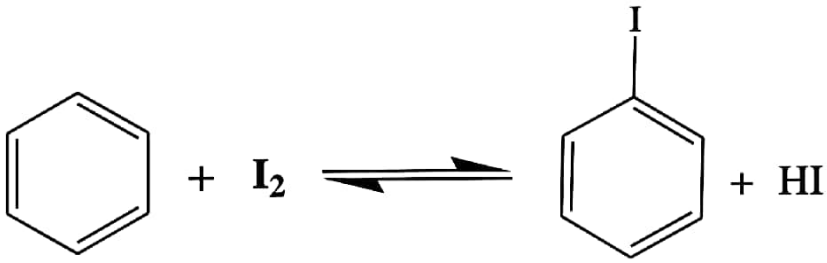
Atom	Electronegativity	Electrophilicity	First Ionization Energy (kJ/mol)
Fluorine	4.0	3.86	1681
Chlorine	3.0	3.67	1251
Bromine	2.8	3.40	1140
Iodine	2.5	3.09	1008

- Controlled fluorination of benzene is difficult, but it can be accomplished by a two-step **THALLATION PROCEDURE**. Benzene reacts with **thallium tris** [**trifluoroacetate, $Tl(OCOCF_3)_3$**] to give an **organothallium** intermediate. Further reaction with **potassium fluoride** and **boron trifluoride** gives the **aryl fluoride**.





- This is because, when **Iodine** adds to the **Benzene** reversibly generating **HI**. **HI** being a strong reducing agent regenerates "**I**" from **aryl iodide** giving back the **aromatic hydrocarbon**. However, in the presence of oxidizing agents such as **HIO_3**, **HI** is converted back to **Iodine** thereby increasing the concentration of **Iodine** in the reaction mixture. <u>According to *Le-Chatelier's principle*, if the concentration of one of the reagents is increased then the equilibrium shifts in the forward direction to give aryl iodide as the desired product.</u>



a) Oxidizing agents (HIO_3, HNO_3) reconverts **HI** to I_2

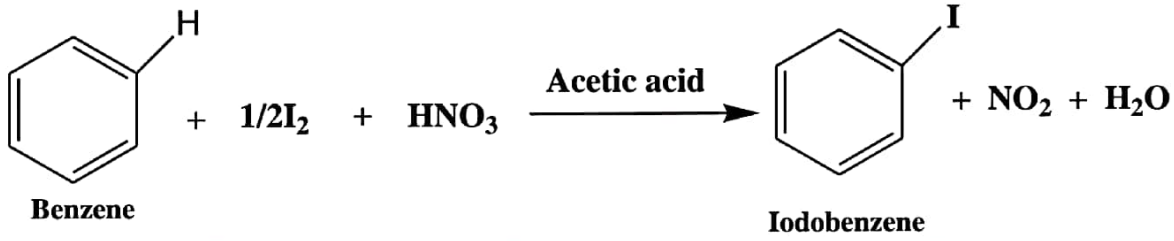
$$5HI + HIO_3 \longrightarrow 3I_2 + 3H_2O \quad | \quad 2HI + 2HNO_3 \longrightarrow I_2 + 2H_2O + 2NO_2$$

- Another way to obtain aryl iodide is to remove HI as soon as it is formed in the reaction mixture, by forming salts. For example, when the Mercuric oxide is used, it converts Hydrogen Iodide to Mercuric Iodide that is then discarded.

b) Salt formation (alkali hydroxide, carbonate or hydrogen carbonate, borax, HgO, Hg-acetate or aliphatic amine or Ammonia)

$$2HI + HgO \longrightarrow HgI_2 + H_2O$$

- **The reaction mechanism of Iodination of benzene**
  - Oxidizing agents, when used, **Iodine** (I_2) get oxidize to **iodonium ion** (I^+) by using HNO_3 or H_2SO_4 in the presence of **Acetic acid** and this reaction was called **Tronov-Novikov reaction**.
  - **Iodine** can be easily oxidized by using **nitric acid** (HNO_3) in the presence of an **Acetic acid** and **Iodine** generates **Iodine cation** that reacts with Benzene giving **Iodobenzene**, **Nitrogen dioxide**, and **water**.
  - Here HNO_3 is consumed in the reaction; hence it is a **reagent** and not a **catalyst**.
  - Reaction mechanism:



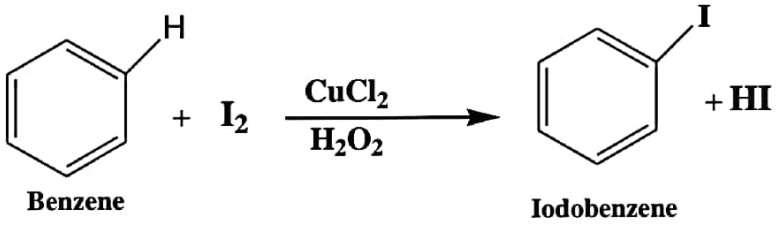
Generate of iodonium ion (I^+)

$$H^+ + HNO_3 + 1/2I_2 \longrightarrow I^+ + NO_2 + H_2O$$

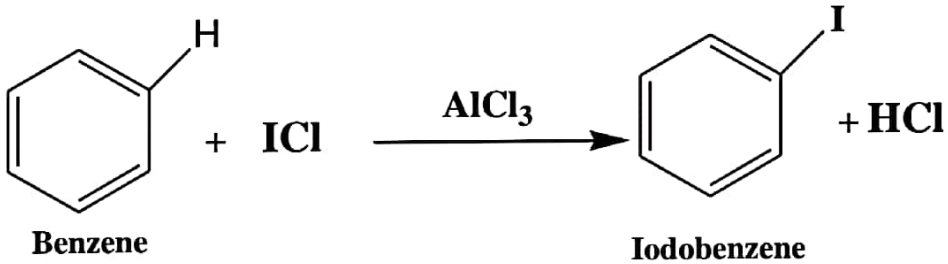
Iodine cation

$I_2 + HNO_3 + \text{Acetic acid } (H^+) \longrightarrow$ ***Tronov-Novikov Method***

  - A similar mechanism is seen for **Cupric Chloride** and **Hydrogen peroxide** for generation of Iodine cation.

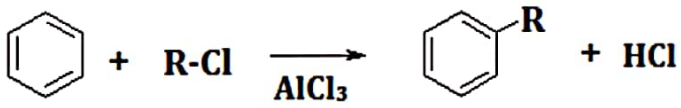


  - The best reagent for Iodination is **Iodine monochloride** (**ICl**) an interhalogen compound. **Chlorine** is more electronegative and pulls the electron cloud towards itself giving **Iodine** a (delta) positive charge. The Benzene ring can pick up this quickly than Iodine from the non-polar I bond thereby giving **aryl iodide** as the desired product.

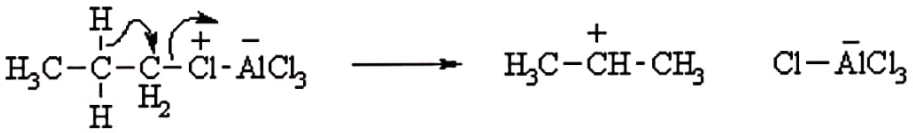


5. FRIEDEL-CRAFTS ALKYLATION OF BENZENE

- Alkylation means substituting an alkyl group into something - in this case into a benzene ring. A hydrogen on the ring is replaced by a group like methyl or ethyl and so on. Benzene is treated with a chloroalkane (for example, chloromethane or chloroethane) in the presence of aluminium chloride as a catalyst.
- **Reaction type:** Electrophilic Aromatic Substitution
- **General Reaction:**



- Named after **Friedel** and **Crafts** who discovered the reaction in 1877.
- **Reagent:** normally the alkyl halide (e.g. R-Br or R-Cl) with aluminum trichloride, $AlCl_3$, a Lewis acid catalyst
- The $AlCl_3$ enhances the electrophilicity of the alkyl halide by complexing with the halide
- **Electrophilic species:** the carbocation (R^+) formed by the "removal" of the halide by the Lewis acid catalyst
- The reactive electrophile, the carbocation is prone to rearrangement to a more stable carbocation which will then undergo the alkylation reaction.



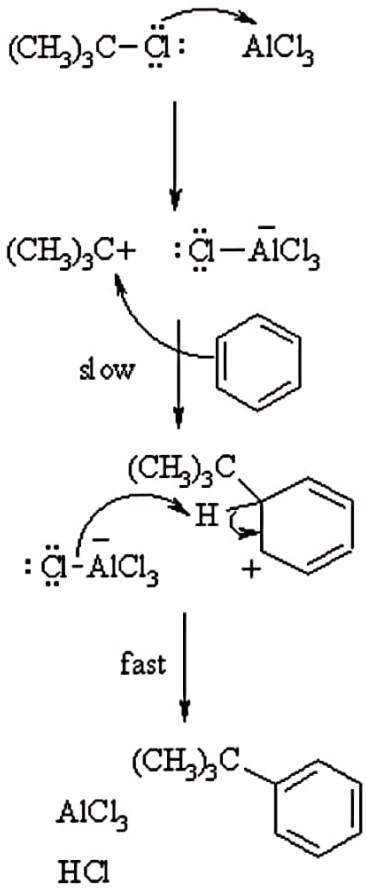
"1°" carbocation 2° carbocation

- **Mechanism for the Friedel-Crafts Alkylation of Benzene**

Step 1:
The alkyl halide reacts with the Lewis acid to form a more electrophilic a **carbocation**

Step 2:
The **p** electrons of the aromatic **C=C** act as a nucleophile, attacking the electrophilic **C⁺**. This step destroys the aromaticity giving the cyclohexadienyl cation intermediate.

Step 3:
Removal of the proton from the **sp^3 C** bearing the alkyl-group reforms the **C=C** and the aromatic system, generating **HCl** and regenerating the active catalyst.



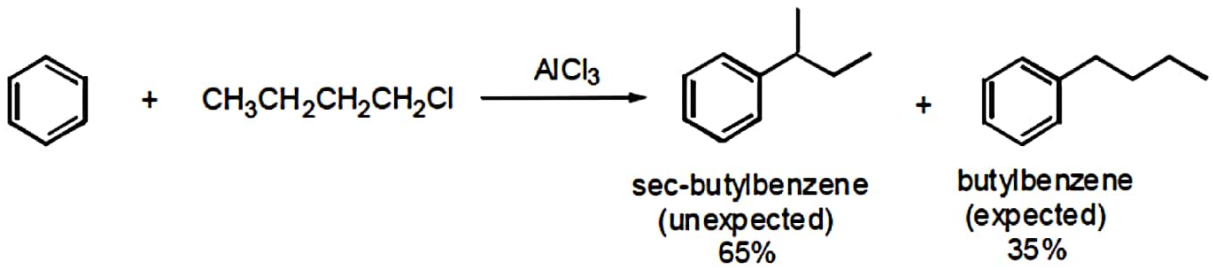
- **THE FRIEDEL-CRAFTS ALKYLATION AND ITS LIMITATIONS**

- The Friedel-Crafts reaction is a convenient way to introduce alkyl groups in the benzene ring. It is a typical electrophilic substitution process, in which the electrophile is (in most cases) a carbocation.
- There are three ways to generate the carbocationic species:

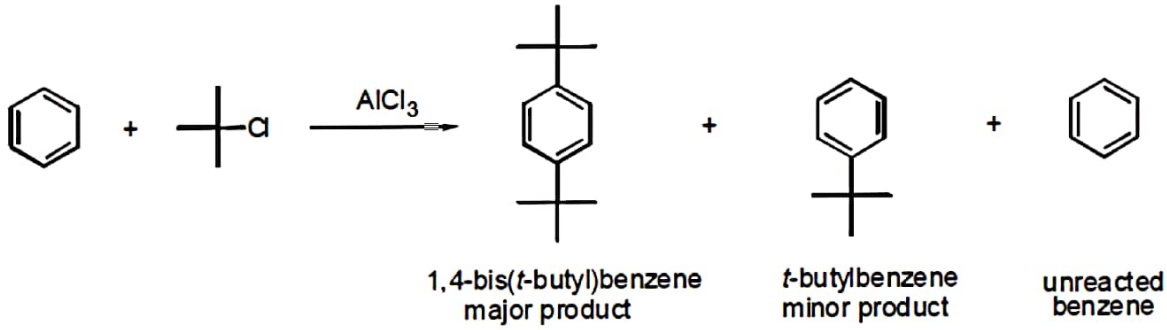
i. *Via preliminary reaction* of an alkyl chloride with $AlCl_3$.
ii. *Via preliminary reaction* of an alcohol with a Lewis acid (such as BF_3) or a Bronsted acid (usually H_3PO_4).
iii. *Via preliminary reaction* of an alkene with a Bronsted acid, whose anion is a weak nucleophile (HF)

- Four strict limitations for Friedel-Crafts Alkylation:

i. The reaction works only with benzene or ACTIVATED benzene derivatives. It will not occur if the benzene ring is DEACTIVATED.
ii. The reaction works only with ALKYL halides (i.e. chlorides, bromides or iodides), but it does not work with VINYL or ARYL halides.
iii. Because of the intermediate formation of carbocations, product mixtures might be obtained, due to rearrangements of the carbocations.

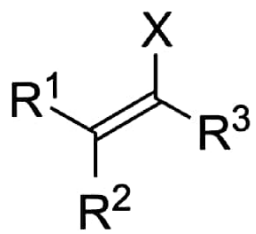


iv. The Friedel-Crafts reaction often leads to the introduction of more than one alkyl group in the molecule. The reason for such undesired polyalkylation

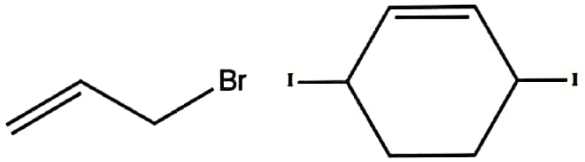


Note By:

VINYL HALIDE: In organic chemistry, a vinyl halide is any alkene with at least one halide substituent bonded directly on one of the alkene carbons.

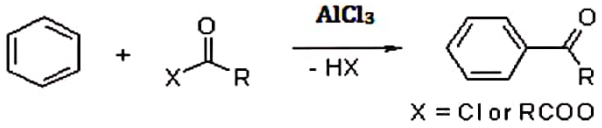


An **ALLYLIC HALIDE** is an alkyl halide in which there is one or more halogen atoms on an allylic carbon. Allylic carbons are carbons bonded to carbon atoms that are doubly bonded to other carbon atoms

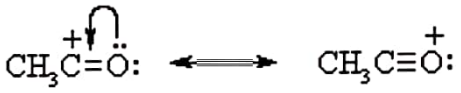


6. FRIEDEL-CRAFTS ACYLATION OF BENZENE

- **Friedel-Crafts Acylation** allows to synthesis of **monoacylated products** from the reaction between **arenes** and **acyl chlorides** or anhydrides. The products are deactivated, and do not undergo a **second substitution.**
- **General Reaction:**



- **Reaction type:** Electrophilic Aromatic Substitution.
- **Reagent:** normally the **acyl halide** (**RCOCl**) with **aluminum trichloride** ($AlCl_3$) which acts as a Lewis acid catalyst.
- Alternatively, the **acid anhydride** [$(RCO)_2O$] can be used instead of the **acyl halide**.
- The $AlCl_3$ enhances the electrophilicity of the acyl halide by complexing with the halide.
- **Electrophilic species:** the **acyl cation** or **acylium ion** (RCO^+) formed by the "removal" of the halide by the *Lewis acid catalyst*
- The **acylium ion** is stabilized by resonance as shown below. This extra stability prevents the problems associated with the rearrangement of simple **carbocations**:



acylium ion

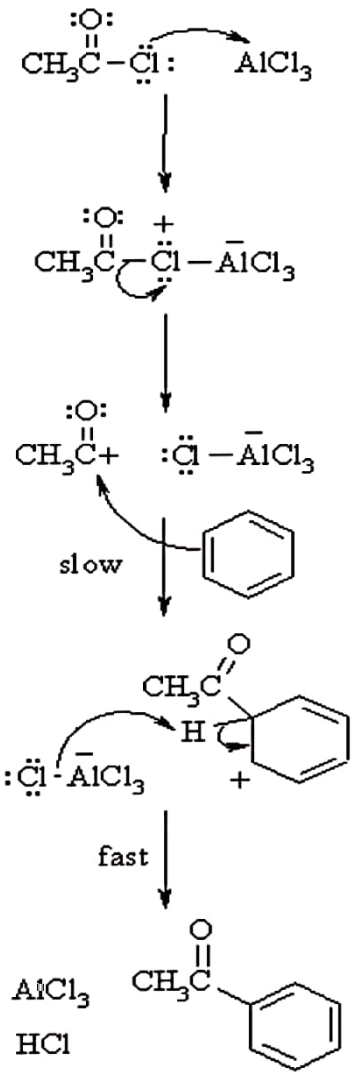
- **Mechanism for the Friedel-Crafts Acylation of Benzene**

Step 1:
The acyl halide reacts with the Lewis acid to form a complex.

Step 2:
Loss of the halide to the Lewis acid forms the electrophilic acylium ion.

Step 3:
The ***p electrons*** of the aromatic **C=C** act as a nucleophile, attacking the electrophilic **C+**. This step destroys the aromaticity giving the cyclohexadienyl cation intermediate.

Step 4:
Removal of the proton from the sp3 C bearing the acyl- group reforms the **C=C** and the aromatic system, generating HCl and regenerating the active catalyst.



SIR CHARLES FRIEDEL

- *Sir Charles Friedel* (12 March 1832 – 20 April 1899) was a French chemist and mineralogist.
- A native of Strasbourg, France.
- He was a student of Louis Pasteur at the Sorbonne.
- In 1876, he became a professor of chemistry and mineralogy at the Sorbonne.
- Friedel developed the **Friedel-Crafts alkylation** and **acylation** reactions with James Crafts in 1877and attempted to make synthetic diamonds.
- His son Georges Friedel (1865–1933) also became a renowned mineralogist.

SIR JAMES CRAFTS

- *Sir James Mason Crafts* (March 8, 1839 – June 20, 1917) was an American chemist, best known for developing the **Friedel-Crafts alkylation** and **acylation** reactions with Charles Friedel in 1876.
- He was born in Boston, Massachusetts and graduated from Harvard University in 1858. Although **he never received his Ph.D.**, he studied chemistry in Germany at the Academy of Mines (1859) of Freiberg

P16CH31 / ORGANIC CHEMISTRY II

UNIT IV: Heterocycles

Heterocyclic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of **heterocycles**.

A **heterocyclic compound** is a cyclic compound at least two different elements as members of its ring(s).

Examples: Nucleic acids, biomass, dyes. 59% of US FDA-approved drugs

Nomenclature: Trivial Names

- A trivial name is a non-systematic name for a chemical substance.
- A trivial name is not a formal name and is usually a common name.
- The names could be based on the appearance of the substance, including all five senses. Some names are based on their use.
- In organic chemistry, some trivial names derive from a notable property of the thing being named. For example, "tartaric acid", a compound found in wine, has a systematic name of 2,3-dihydroxybutanedioic acid.

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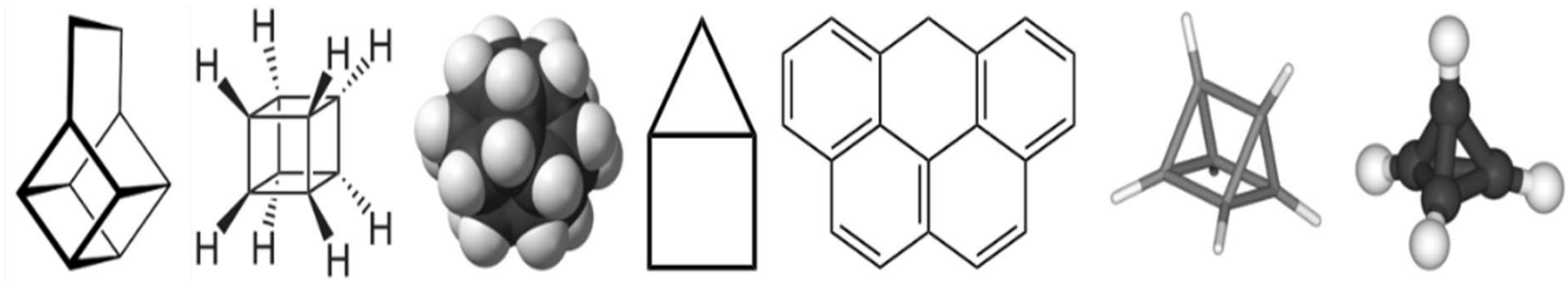
- Several organic molecules have semi-trivial names where the suffixes *-ane* (for an alkane) or *-ene* (for an alkene) are added to a name based on the shape of the molecule. Some are pictured below.



Components are named based on fiction (characters):
Alcindoromycin (Alcindoro),
Collinemycin (Colline),
Marcellomycin (Marcello),
Mimimycin (Mimi),
Musettamycin (Musetta),
Rudolphomycin (Rodolfo) and
Schaunardimycin (Schaunard).

Systematic Names

- A systematic name is a name given in a systematic way to one unique group, organism, object or chemical substance, out of a specific population or collection. Systematic names are usually part of a nomenclature.
- A semisystematic name or semitrivial name is a name that has at least one systematic part and at least one trivial part.
- In chemistry, a systematic name describes the chemical structure of a chemical substance, thus giving some information about its chemical properties.

There are standardized systematic or semi-systematic names for:
Chemical elements (following IUPAC guidelines)
Chemical nomenclature (following IUPAC guidelines)
Binomial nomenclature, initiated by Carl Linnaeus
Astronomical objects and entities (administered by the International Astronomical Union)
Genes (following HUGO Gene Nomenclature Committee procedures)
Proteins
Minerals (administered by the IMA)
Monoclonal antibodies

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The IUPAC defines systematic name as "a name composed wholly of specially coined or selected syllables, with or without numerical prefixes; e.g. pentane, oxazole.“
However, when trivial names have become part of chemical nomenclature, they can be the systematic name of a substance or part of it.
Examples for some systematic names that have trivial origins are benzene (cyclohexatriene) or glycerol (trihydroxypropane).

Replacement nomenclature

The naming heterocyclic compounds carbon atoms of their hydrocarbon analogues are replaced by hetero atoms

Replacement nomenclature can be applied to acyclic structures whether or not cyclic components are attached to them.

Difficult to apply in the naming of chains containing hetero atoms.

R-1.2.2 Replacement operation

The replacement operation involves the exchange of one group of atom or a single nonhydrogen atom for another. This can be expressed in several ways as follow:

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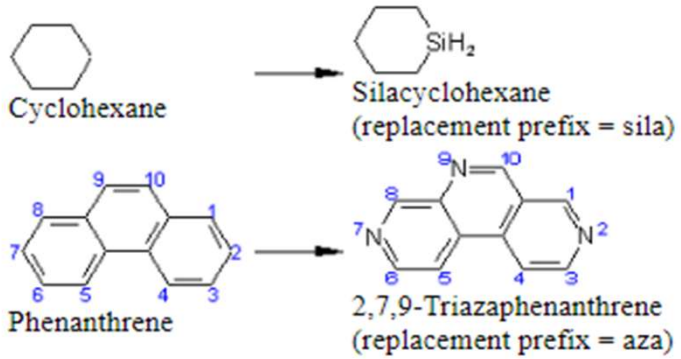
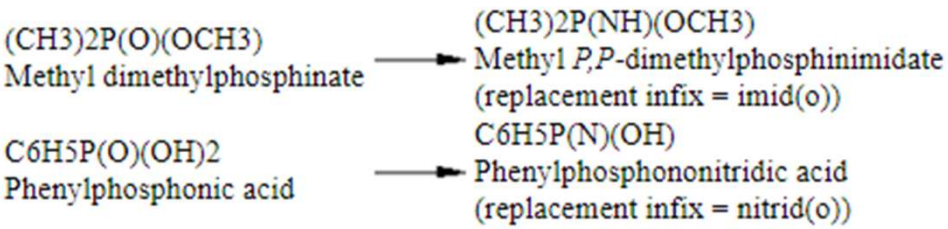
use of "a" prefixes representing the element(s) being introduced

Examples to R-1.2.2.1



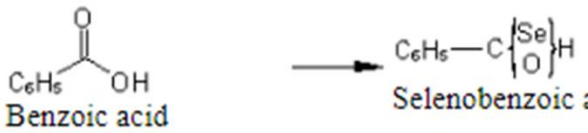
use prefixes or infixes signifying replacement of oxygen atoms or oxygen-containing group

Examples to R-1.2.2.2



The chalcogen affixes "thio-", "seleno-", and "telluro-" indicate replacement of an oxygen atom by another chalcogen atom

Examples to R-1.2.2.2

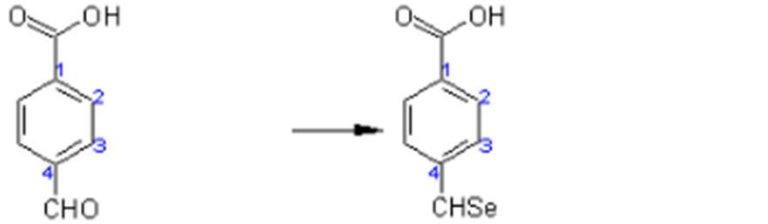


Benzoic acid → Selenobenzoic acid

2*H*-Pyran → 2*H*-Thiopyran

$CH_3—[CH_2]_4—COOH$ → $CH_3—[CH_2]_4—CSSH$

Hexanoic acid → Hexane(dithioic) acid



4-Formylbenzoic acid → 4-(Selenoformyl)benzoic acid

Non-aromatic heterocyclic compounds

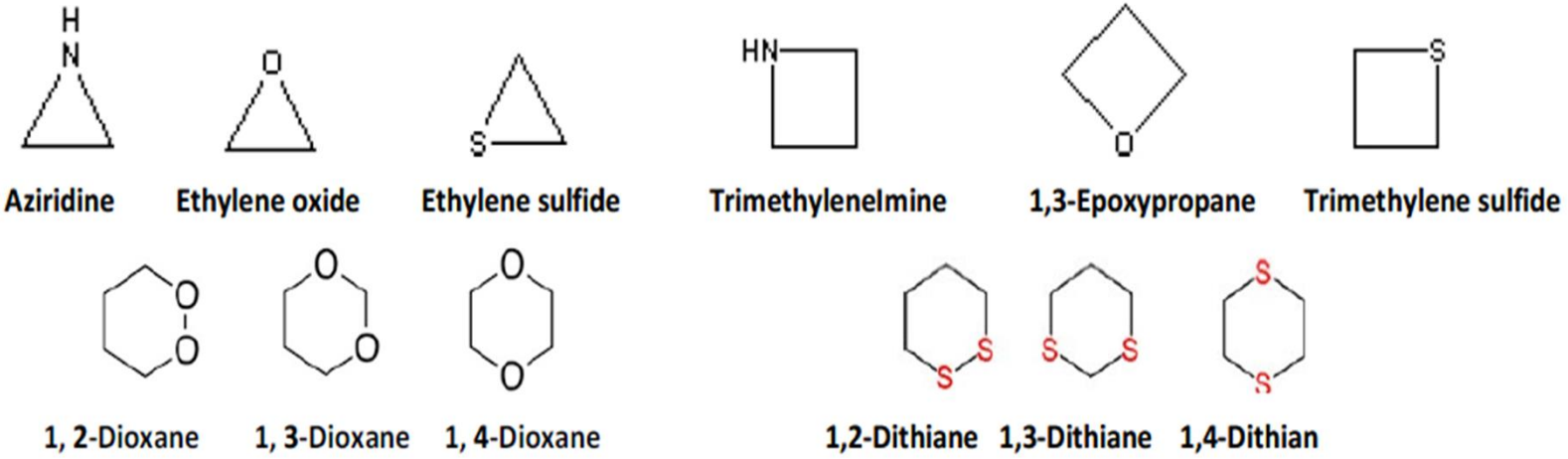
Non-aromatic heterocyclic compounds (without cyclic delocalization) are the cyclic analogs of amines, ethers, amides, enamines, sulfides, etc. and possess many properties common with their acyclic analogs.

Non-aromatic heterocyclic compounds can be further classified as

i) Saturated Non-aromatic Heterocyclic Compounds

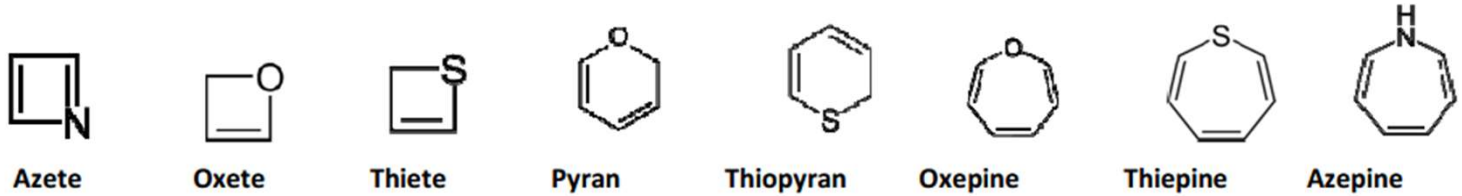
The saturated heterocycles behave like the acyclic derivatives.

(Oxirane), Ethylene Sulfide (Thiirane), TrimethyleneImine (Azetidine), 1,3 Sulfide (Thietane), dioxane (C4H8O2), etc.



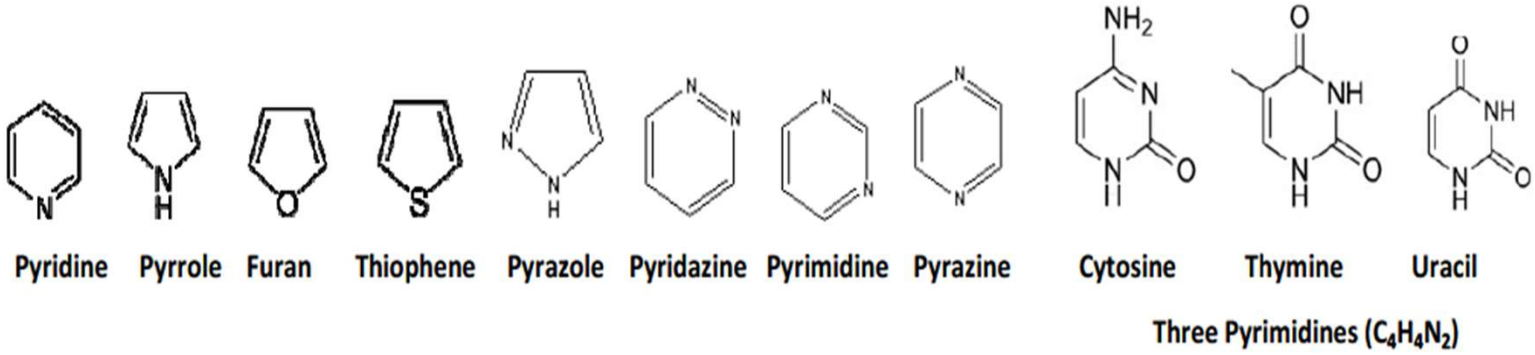
ii) Unsaturated Non-aromatic Heterocyclic Compounds

The unsaturated rings can be classified according to the participation of the heteroatom in the pi system.



Aromatic Heterocyclic Compounds

Aromatic heterocyclic compounds contain one or more atoms other than carbon as part of the aromatic ring.



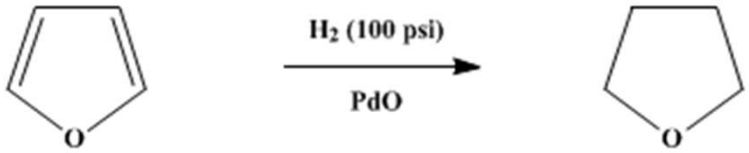
Importance of Heterocyclic compounds:

Heterocyclic compounds are of very much interest in our daily life. They have a wide range of application. The rich activity of these compounds in biological systems is important for pharmaceuticals, agricultural, veterinary and natural products. They also find applications as sanitizers, developers, antioxidants, as corrosion inhibitors, as copolymers, dye stuff. Some of the natural products e.g. antibiotics (such as penicillin), cephalosporin, alkaloids (such as vinblastine), morphine, reserpine etc. have heterocyclic moiety.

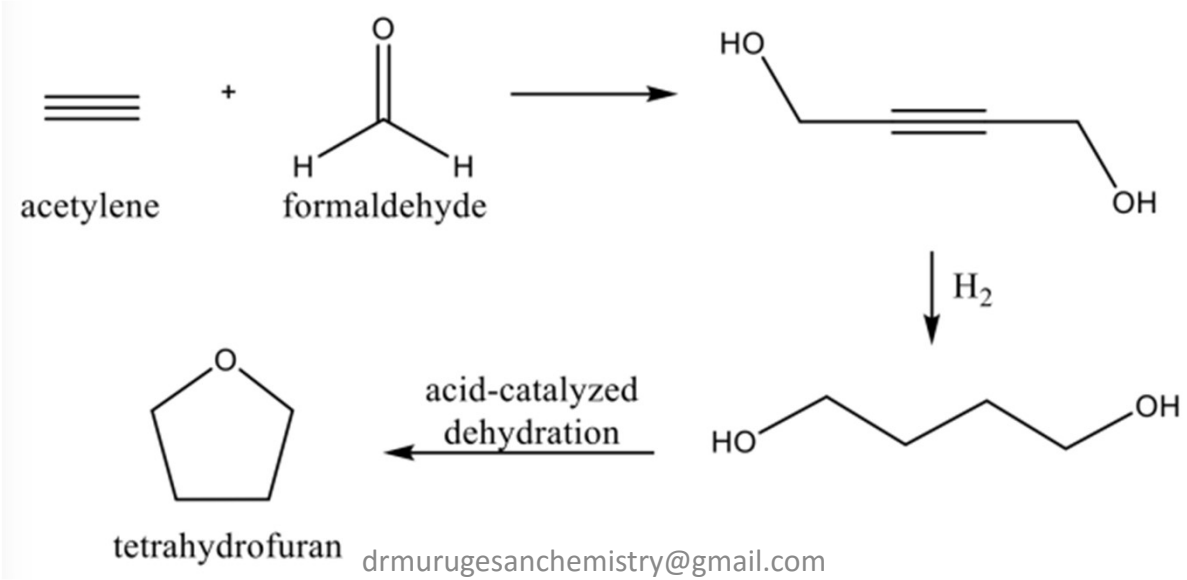
In medicine, aziridine derivatives are used for the treatment of cancer and in research as affinity probes (labeled chemicals that react selectively with biological molecules of interest) for detection and assay studies. The mitomycin family of antitumour antibiotics is the most well-known class of natural products containing the aziridine ring.

Tetrahydrofuran (THF)

Tetrahydrofuran, or oxolane, is an organic compound with the formula $(CH_2)_4O$. It is a colorless. water-miscible organic liquid with low viscosity. It is mainly used as a precursor to polymers.[8] Being polar and having a wide liquid range, THF is a versatile solvent.



Industrial production of THF involves reaction of formaldehyde with acetylene to make 2-butyne-1,4-diol. This intermediate is hydrogenated and cyclised in two more steps to yield THF.



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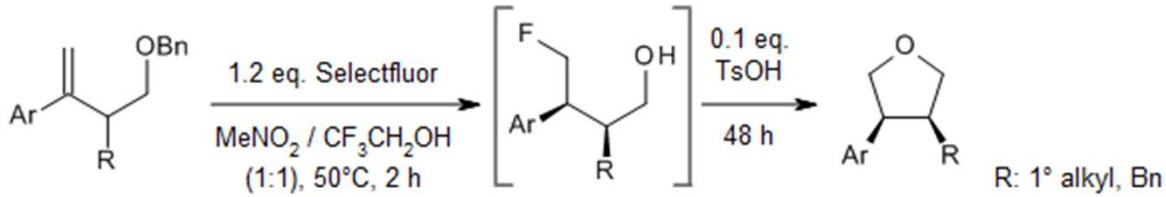
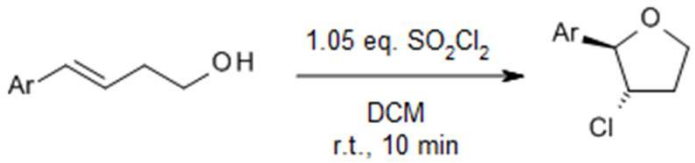
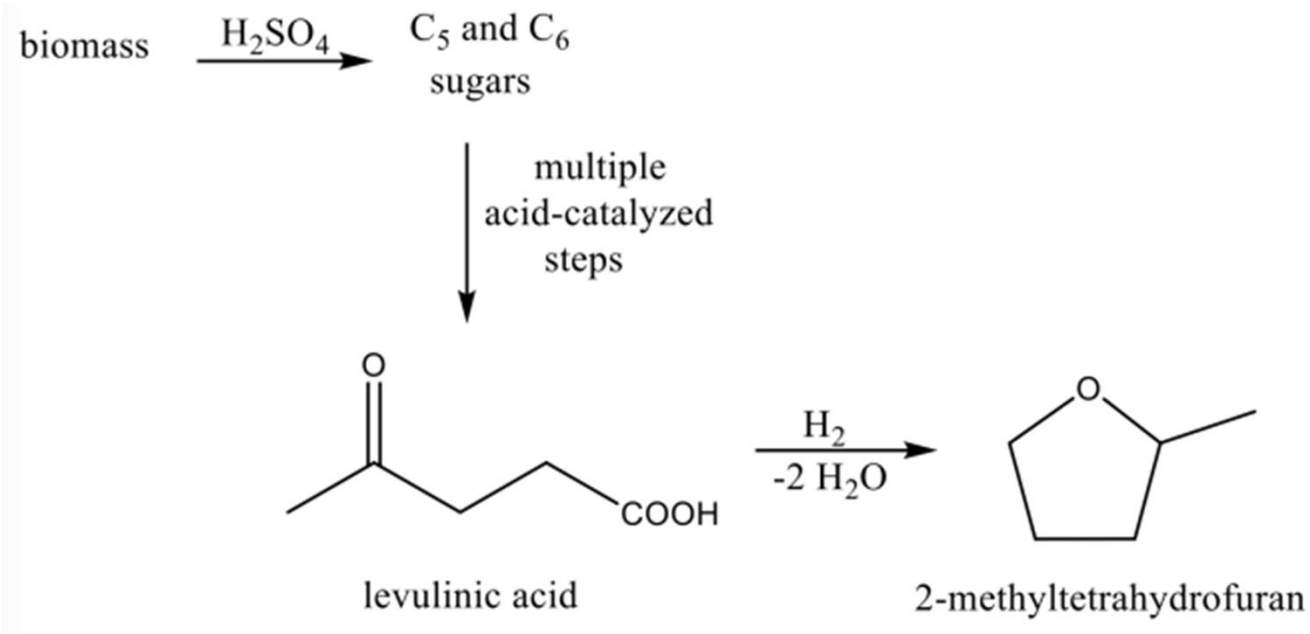
Electrophilic bromination or fluorination of homoallylic alcohol O-Bn ethers triggers a diastereoselective hydride transfer to provide diastereomerically enriched haloalkyl alcohols. A subsequent intramolecular nucleophilic substitution affords tetrahydrofurans.



Sulfuryl chloride as chlorinating agent enables an efficient, mild and catalyst-free synthesis of β-chlorotetrahydrofuran derivatives by 5-*endo* chlorocycloetherification of homoallylic alcohols. A variety of homoallylic alcohols with aryl or alkyl substituents were smoothly converted into β-chlorotetrahydrofurans in very good yields.



An alternative to THF is 2-methyltetrahydrofuran, which has a very similar structure to THF. It can be synthesized starting from biomass; after conversion to C_5 and C_6 sugars and subsequent acid-catalyzed steps, the intermediate levulinic acid can be hydrogenated to yield 2-methyl THF.



levulinic acid

2-methyltetrahydrofuran

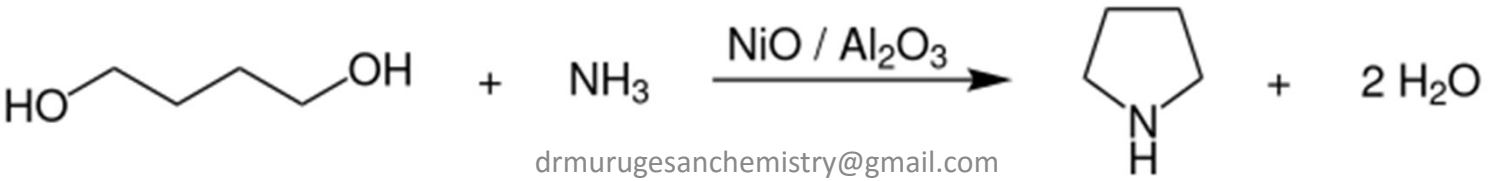
Pyrrolidine

Pyrrolidine, also known as tetrahydropyrrole, is an organic compound with the molecular formula $(CH_2)_4NH$. It is a cyclic secondary amine, also classified as a saturated heterocycle. It is a colourless liquid that is miscible with water and most organic solvents. It has a characteristic odor that has been described as "ammoniacal, fishy, shellfish-like".

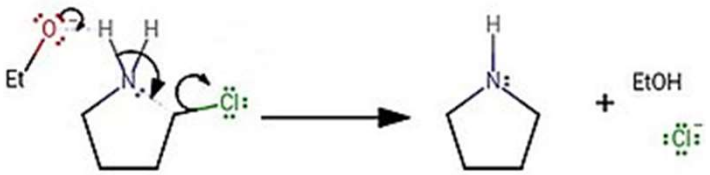
The pyrrolidine ring structure is present in numerous natural alkaloids such as nicotine and hygrine. It is found in many drugs such as procyclidine and bepridil.

Industrial production

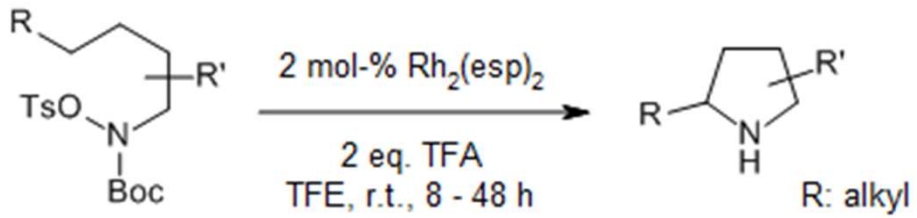
Pyrrolidine is prepared industrially by the reaction of 1,4-Butanediol and ammonia at a temperature of 165–200 °C and a pressure of 17–21 MPa in the presence of a cobalt- and nickel oxide catalyst, which is supported on alumina.



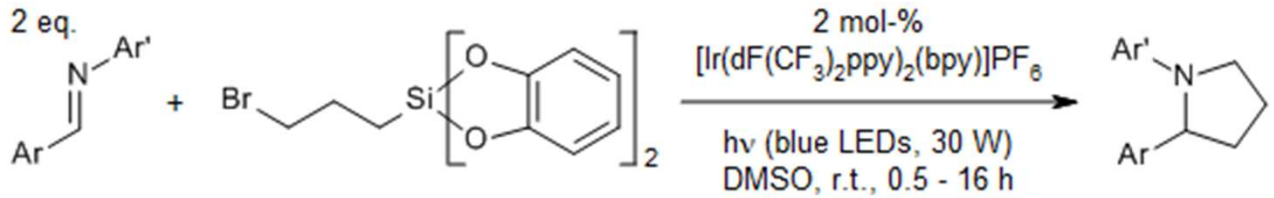
In the laboratory, pyrrolidine was usually synthesised by treating 4-chlorobutan-1-amine with a strong base:

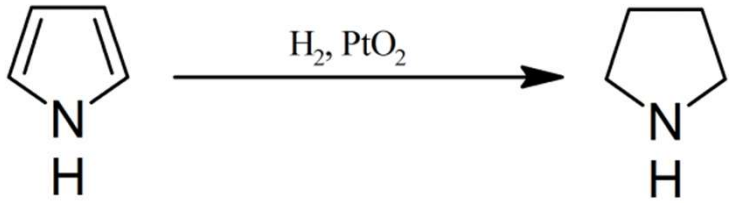


Dirhodium-catalyzed intramolecular nitrene insertion into sp^3 C-H bonds enables a regio- and diastereoselective synthesis of *N*-unprotected pyrrolidines at rt without external oxidants



With the aid of visible light irradiation, the reaction of photocatalytically generated alkyl radicals possessing pendant leaving groups with imines provides substituted pyrrolidines

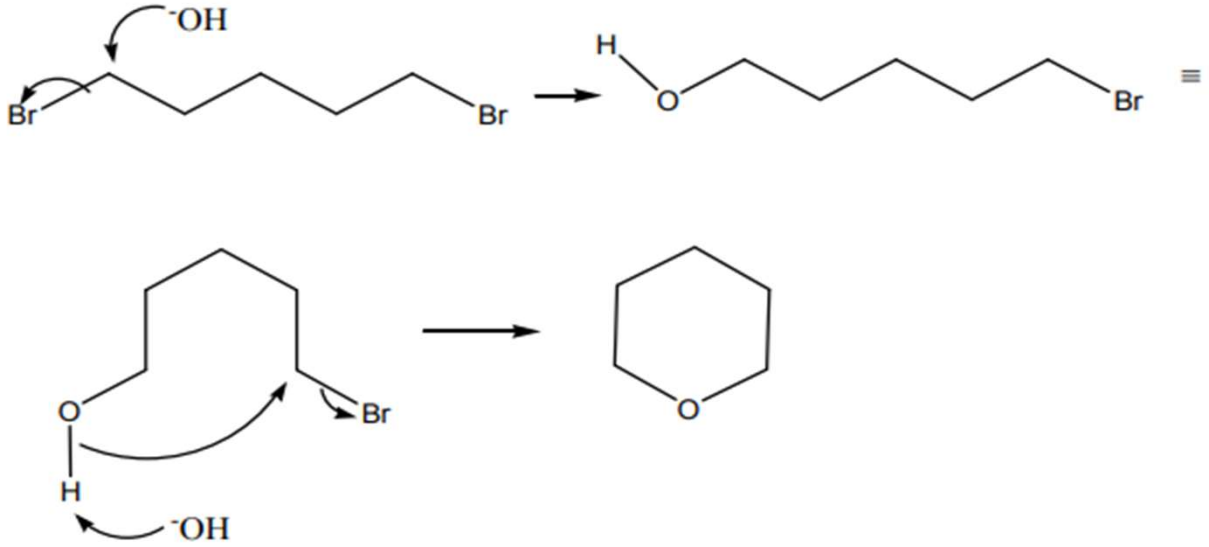




Tetrahydropyran (**THP**)

Tetrahydropyran is the organic compound consisting of a saturated six-membered ring containing five carbon atoms and one oxygen atom. It is named by reference to pyran, which contains two double bonds, and may be produced from it by adding four hydrogens. IUPAC name was established as oxane. The compound is a colourless volatile liquid.

1,5-dibromopentane into oxacyclohexane



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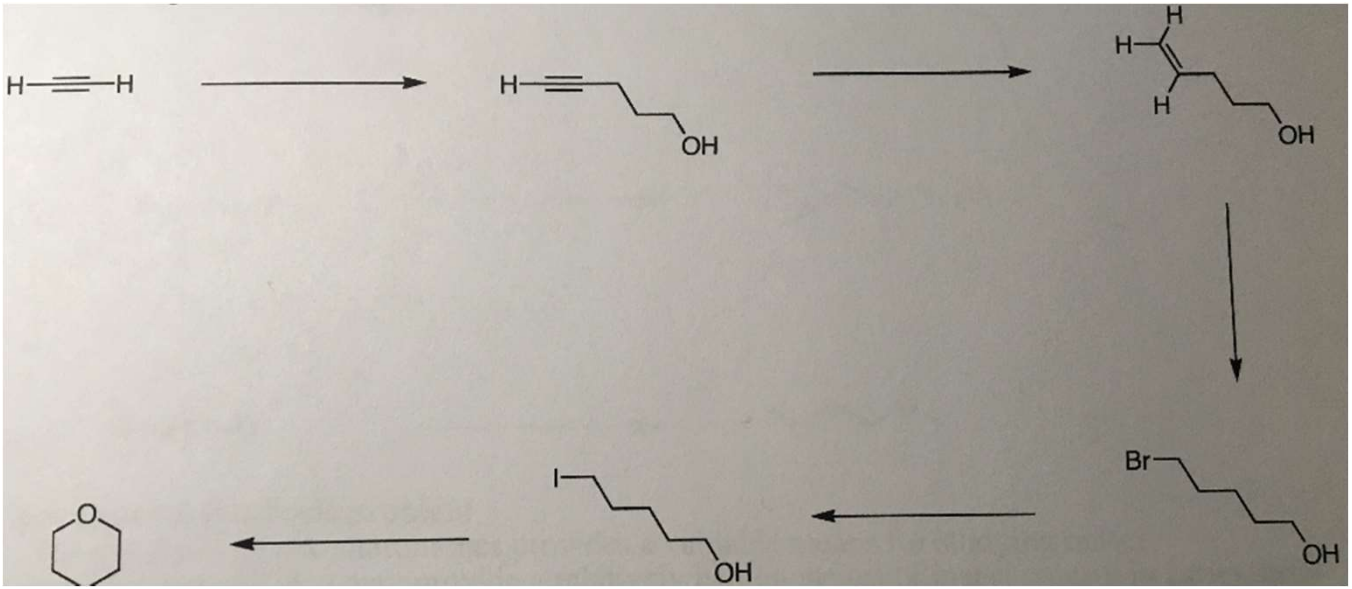

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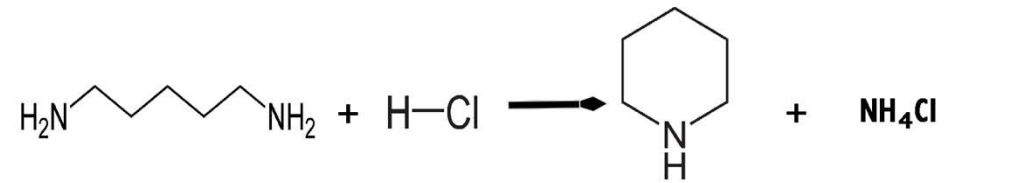
Piperidine

Piperidine is an organic compound with the molecular formula $(CH_2)_5NH$. This heterocyclic amine consists of a six-membered ring containing five methylene bridges ($–CH_2–$) and one amine bridge (–NH–). It is a colorless liquid with an odor described as objectionable, and typical of amines.[6] The name comes from the genus name *Piper*, which is the Latin word for pepper.

Industrially, piperidine is produced by the hydrogenation of pyridine, usually over a molybdenum disulfide catalyst:

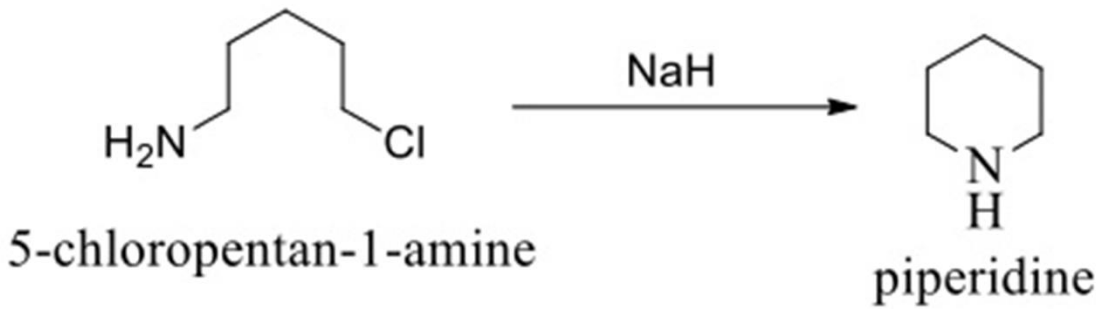
$$C_5H_5N + 3\ H_2 \rightarrow C_5H_{10}NH.$$

Pyridine can also be reduced to piperidine via a modified Birch reduction using sodium in ethanol.



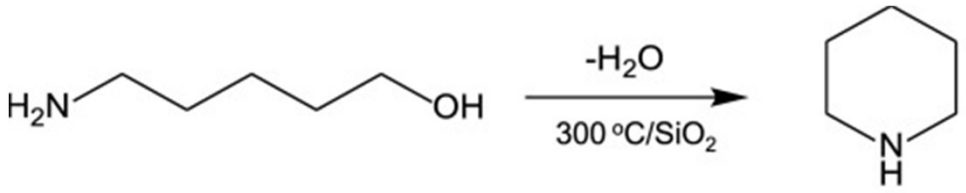
Synthesis of Piperidine

- Cyclization of 1-amino-5-haloalkane



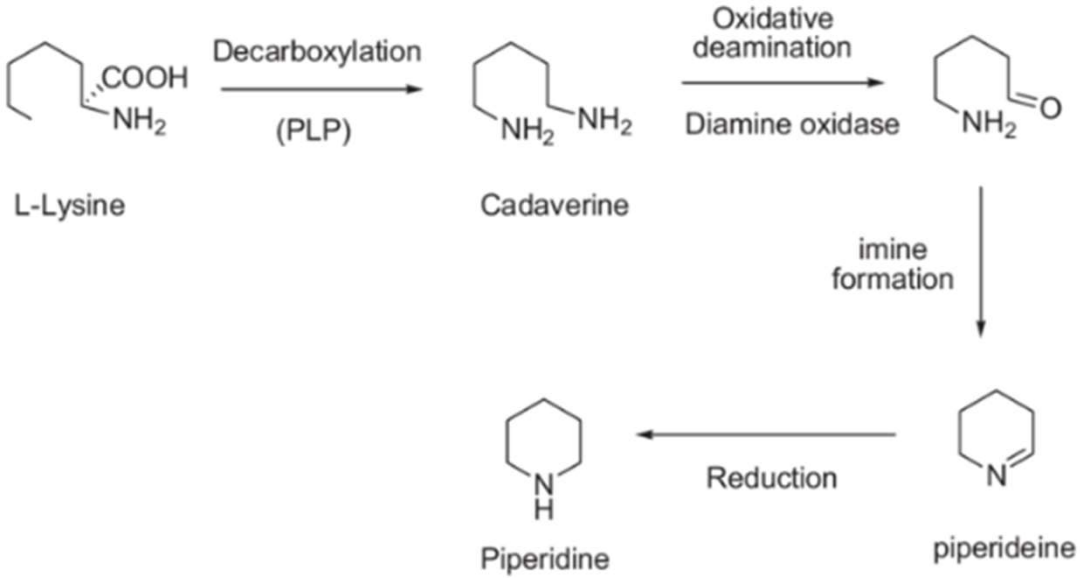
5-chloropentan-1-amine

piperidine



Conversion: 99.9%

Selectivity: 94.8%



L-Lysine

Cadaverine

piperideine

Piperidine

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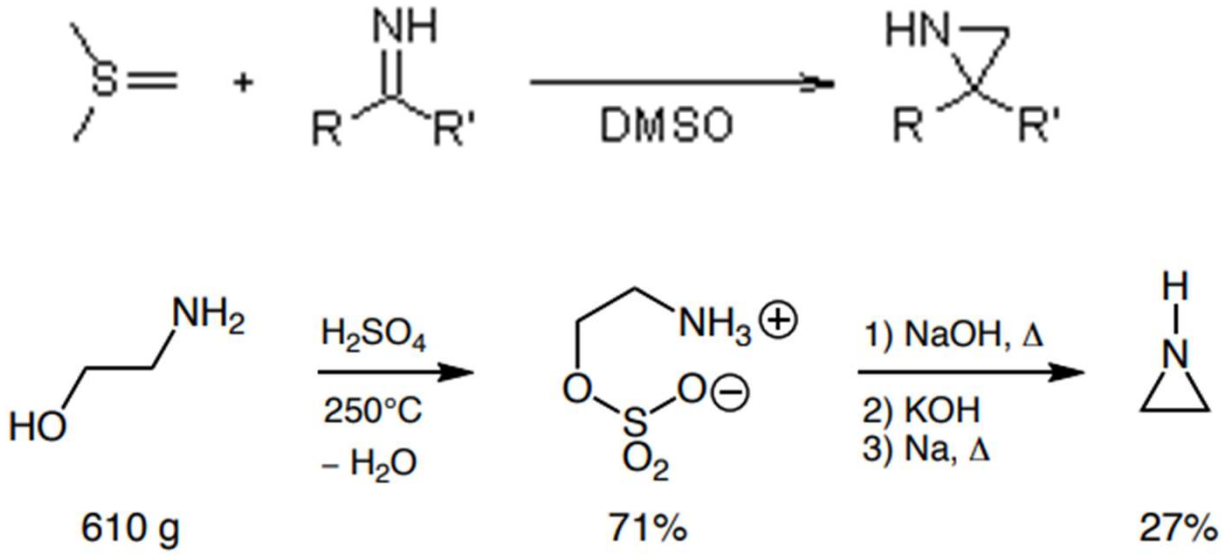
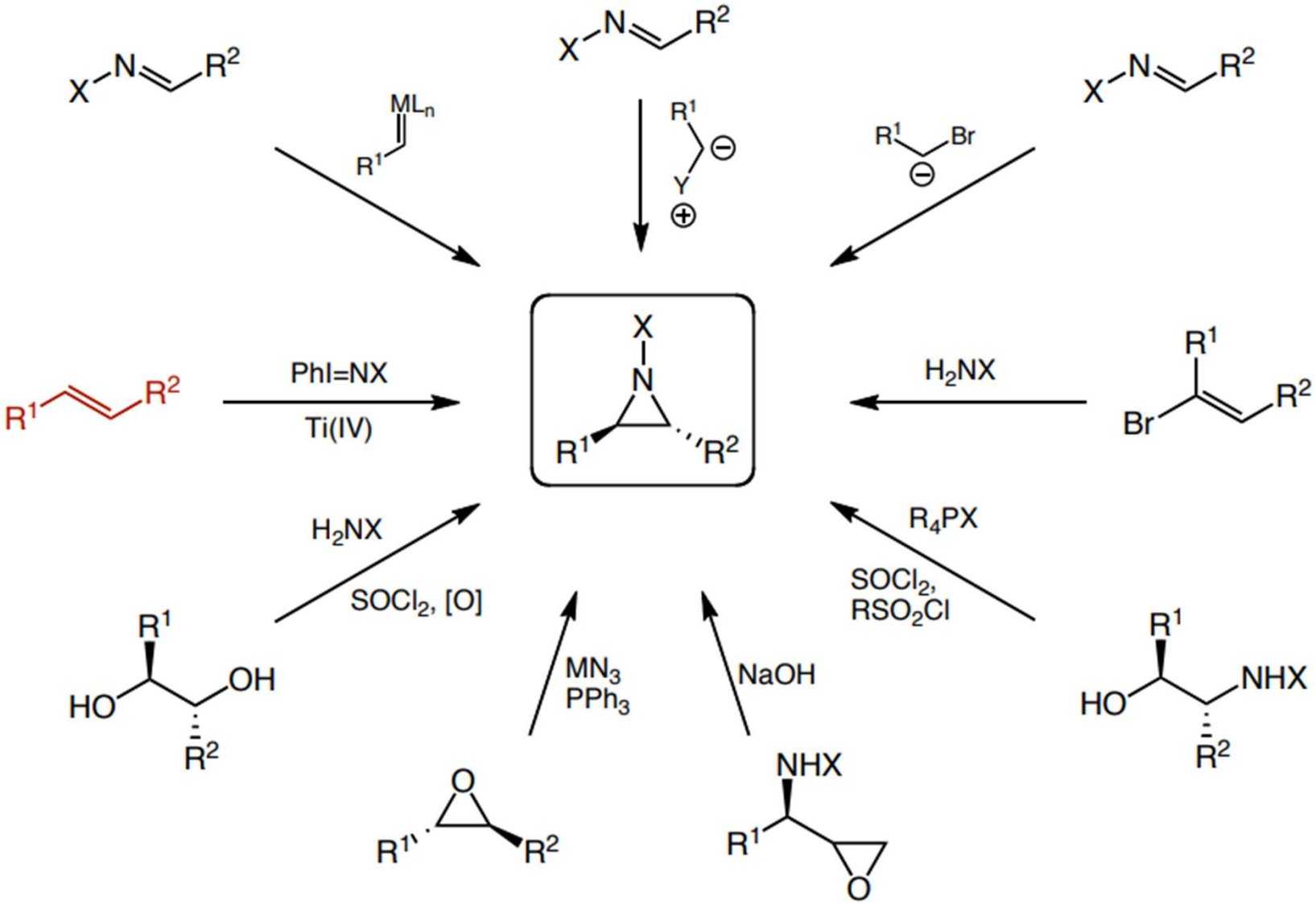
Aziridine

Aziridine is an organic compound consisting of the three-membered heterocycle $(CH_2)_2NH$.[5][6] It is a colorless, toxic, volatile liquid that is of significant practical interest.[7] Its derivatives, also referred to as aziridines, are of broader interest in medicinal chemistry. Aziridine is less basic than acyclic aliphatic amines.

The reaction of sulfurylides with imines leads to the formation of aziridines.



H. Wenker, *J. Am. Chem. Soc.* **1935**, *57*, 2328.



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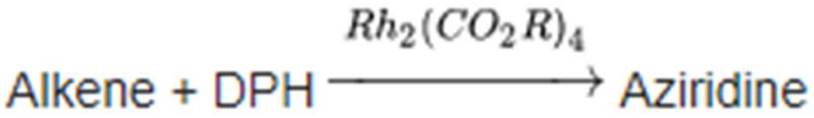
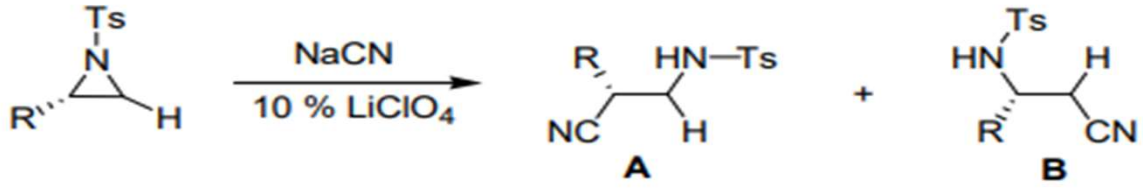
Aziridines are obtained by treating a mono-, di-, tri- or tetra- substituted alkene (olefin) with O-(2,4-dinitrophenyl)hydroxylamine (DPH) in the presence of rhodium catalysis.



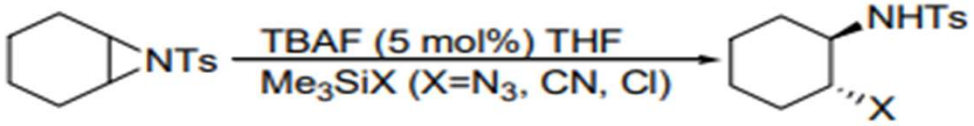
Aziridines are reactive substrates in ring-opening reactions with many nucleophiles due to their ring strain. Alcoholysis and aminolysis are basically the reverse reactions of the cyclizations. Carbon nucleophiles such as organolithium reagents and organocuprates are also effective.

Regioselectivity of aziridine ring opening

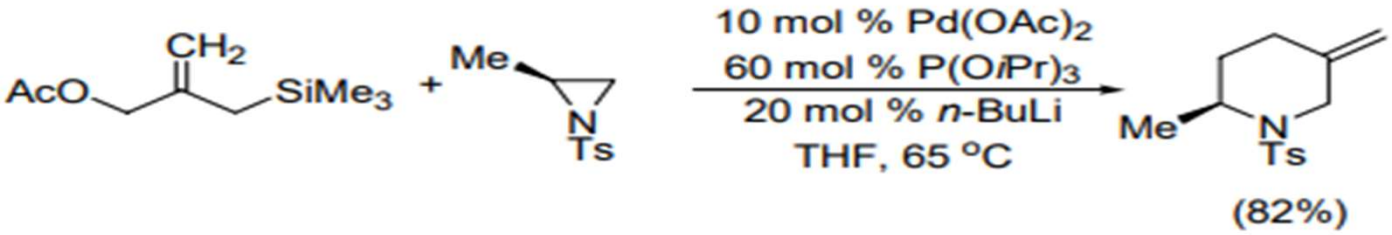


R	Yield(%)	A:B
Ph	90	92:8
n-Bu	87	15:85
n-Oct	83	10:90

TBAF-catalyzed ring-opening



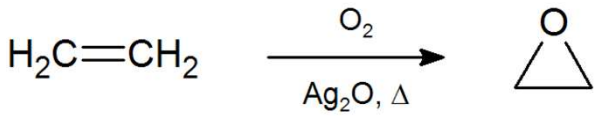
[3+3]-cycloaddtion of aziridines



Oxiranes

Epoxides (also known as oxiranes) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons.

The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air.

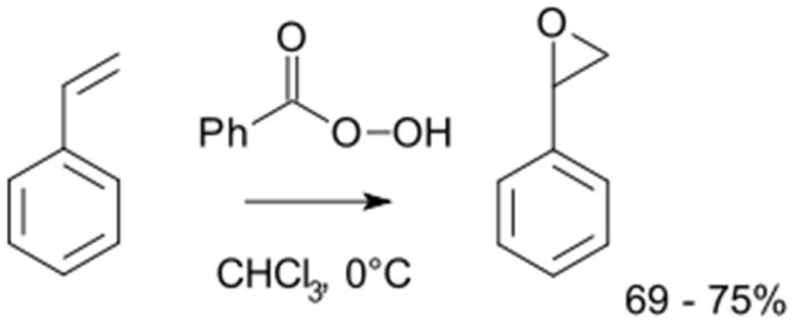


Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. Epoxides are colourless and nonpolar, and often volatile.

The epoxidation of ethylene involves the reaction of oxygen yields oxirane.

$$7\ H_2C{=}CH_2 + 6\ O_2 \rightarrow 6\ C_2H_4O + 2\ CO_2 + 2\ H_2O$$

Prilezhaev reaction approach involves the oxidation of the alkene with a peroxyacid such as m-CPBA. Illustrative is the epoxidation of styrene with perbenzoic acid to styrene oxide



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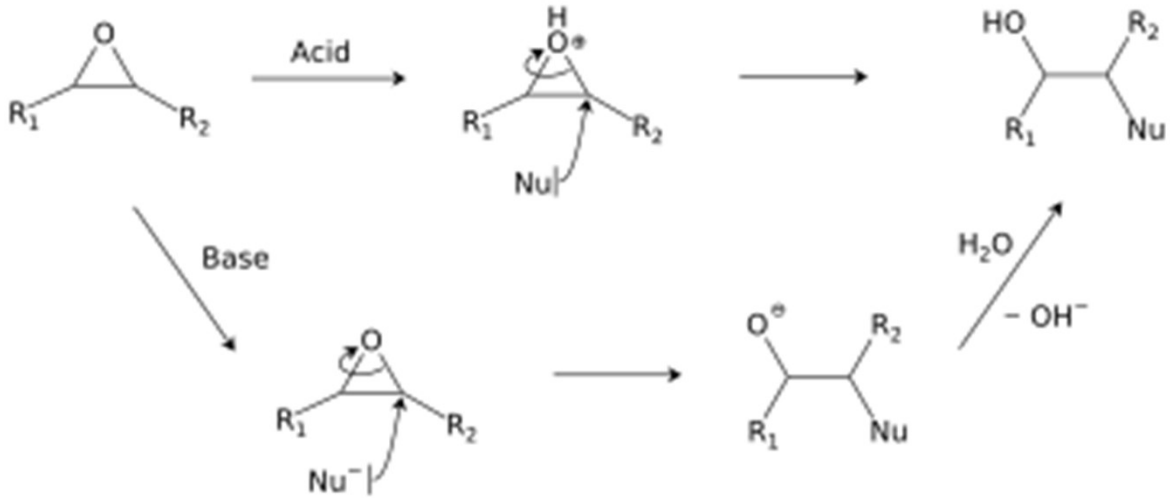
Neucleophilic epoxidation: Electron-deficient olefins, such as enones and acryl derivatives can be epoxidized using nucleophilic oxygen compounds such as peroxides. The reaction is a two-step mechanism. First the oxygen performs a nucleophilic conjugate addition to give a stabilized carbanion. This carbanion then attacks the same oxygen atom, displacing a leaving group from it, to close the epoxide ring.

Bio-synthesis: Epoxides are uncommon in nature. They arise usually via oxygenation of alkenes by the action of cytochrome P450.

Hydrolysis and addition of nucleophiles



Polymerization of epoxides gives polyethers. For example ethylene oxide polymerizes to give polyethylene glycol, also known as polyethylene oxide. The reaction of an alcohol or a phenol with ethylene oxide, ethoxylation, is widely used to produce surfactants:

$$ROH + n\ C_2H_4O \rightarrow R(OC_2H_4)_nOH$$

Deoxygenation: Epoxides can be deoxygenated using oxophilic reagents. This reaction can proceed with loss or retention of configuration. The combination of tungsten hexachloride and *n*-butyllithium gives the alkene.

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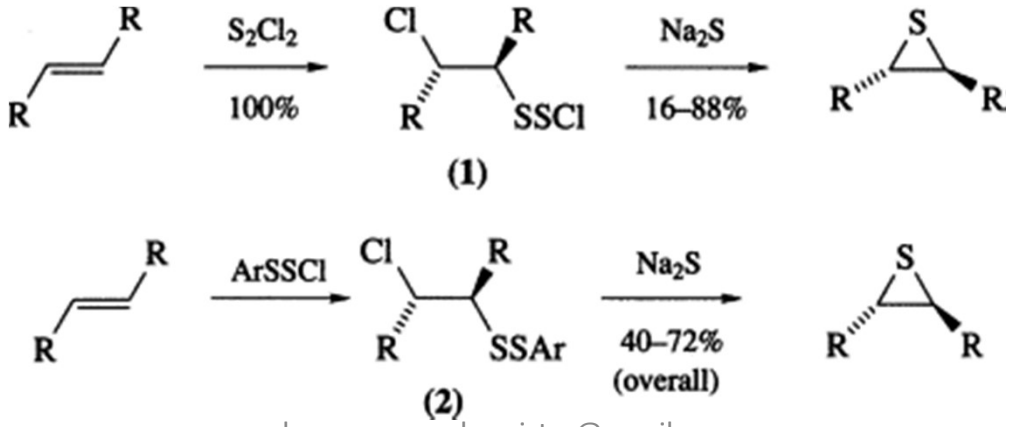
Thiirane

Thiirane, more commonly known as ethylene sulfide, is the cyclic chemical compound with the formula C_2H_4S. The IUPAC name is Thiacyclopropane. It is the smallest sulfur-containing heterocycle and the simplest episulfide.

According to electron diffraction, the C-C and C-S distances in ethylene sulfide are respectively 1.473 and 1.811 Å. The C-C-S and C-S-C angles are respectively 66.0 and 48.0°. Pale, yellow liquid. Boiling point 56 °C.

It can be prepared by the reaction of ethylene carbonate and KSCN. For this purpose the KSCN is first melted under vacuum to remove water.

$$KSCN + C_2H_4O_2CO \rightarrow KOCN + C_2H_4S + CO_2$$



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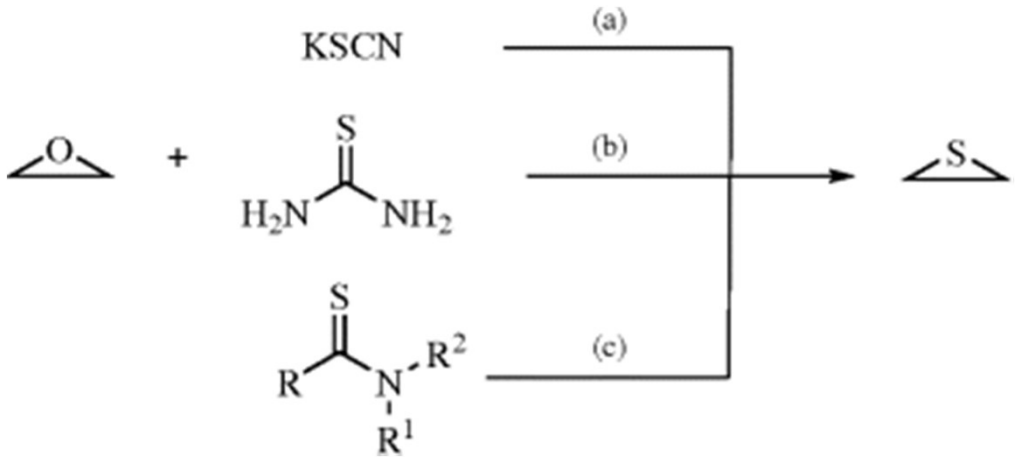


Ethylenesulfide adds to amines to afford 2-mercaptoethylamines, which are good chelating ligands.

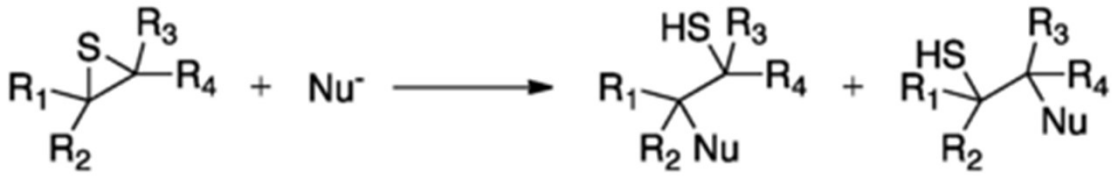
$$C_2H_4S + R_2NH \rightarrow R_2NCH_2CH_2SH$$

This process is often called mercaptoethylation.
Oxidation of thiirane with periodate gives ethylene episulfoxide.

Episulfides in both academic and industrial settings most often involve their use as monomers in polymerization reactions.

Episulfides have an innate ring strain due to the nature of three-membered rings.

Most reactions of episulfides involve ring-opening. Most commonly, nucleophiles are employed for the ring-opening process. For terminal episulfide, nucleophiles attack the primary carbon. Nucleophiles include anionic hydride, thiolates, alkoxide, amines, and carbanions.



Azetidine

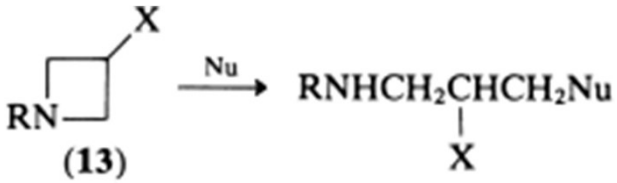
Azetidine (C_3H_7N) is a saturated heterocyclic organic compound containing three carbon atoms and one nitrogen atom. It is a liquid at room temperature with a strong odor of ammonia and is strongly basic compared to most secondary amines. It is also called as Azacyclobutane.

A colorless liquid. Its bioling point is 61 to 62 °C.

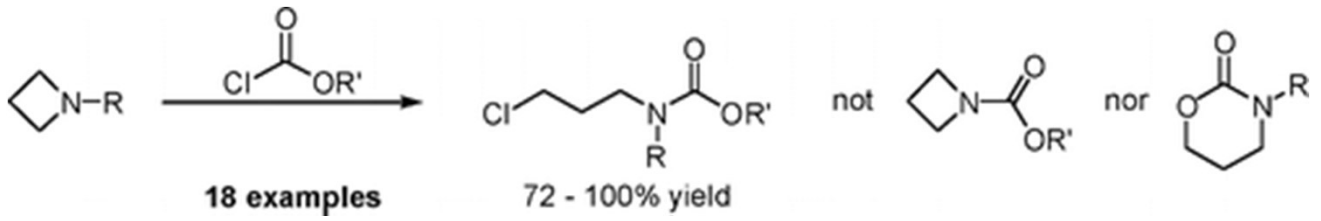
Azetidines can be prepared by reduction of azetidinones (β-lactams) with lithium aluminium hydride.

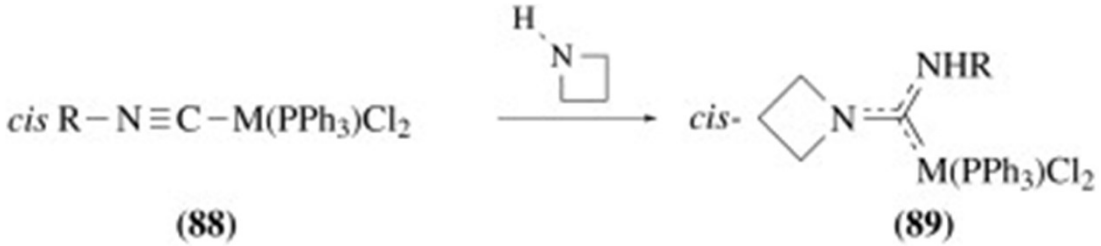
Azetidine can also be produced by a multistep route from 3-amino-1-propanol.

Nucleophilic ring opening of azetidines can proceed in good yield depending on the nucleophile and catalyst. Cleavage of the azetidine ring by nucleophiles under the influence of Lewis acid catalysts .



The reaction of an azetidine with a chloroformate can give either the dealkylated heterocycle or the ring-opened product (γ-chloroamine), which can further cyclize to the oxazinanone.



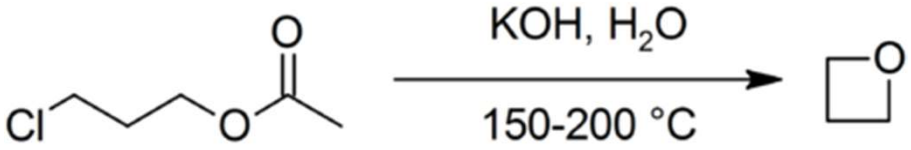


Azetidine reacts with the coordinated isocyanide ligand of the neutral complex and the cationic complex. in THF to form the corresponding diaminocarbene derivatives

Oxetane

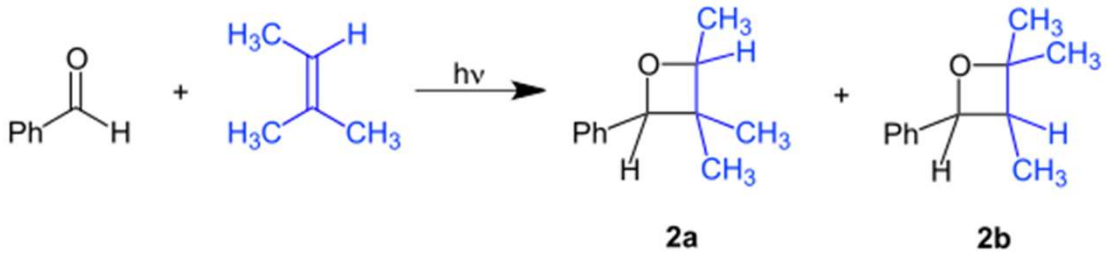
Oxetane, or 1,3-propylene oxide, is a heterocyclic organic compound with the molecular formula C_3H_6O, having a four-membered ring with three carbon atoms and one oxygen atom.

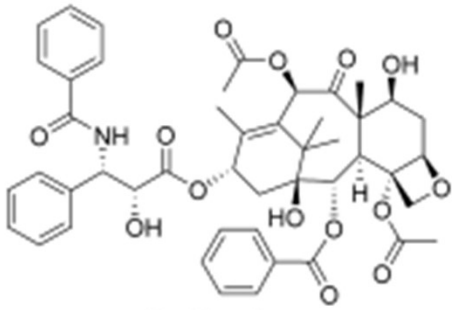
A typical well-known method of preparation is the reaction of potassium hydroxide with 3-chloropropyl acetate at 150 °C:

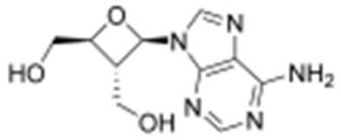


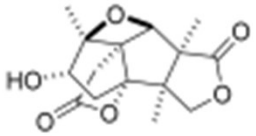
Yield of oxetane made this way is c. 40%, as the synthesis can lead to a variety of by-products.

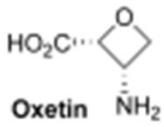
Other possible reactions to form oxetane ring is the Paternò–Büchi reaction. The oxetane ring can also be formed through diol cyclization as well as through decarboxylation of a six-membered cyclic carbonate.

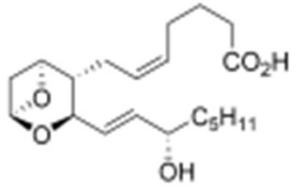


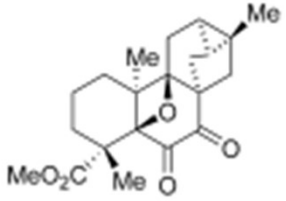

Paclitaxel

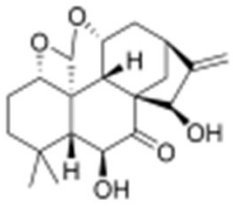

Oxetanocin A

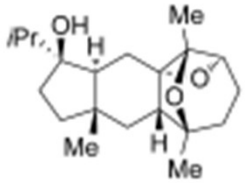

Merrilactone A


Oxetin


Thromboxane A_2


Mitrephorone A


Maoyecrystal I


Dictyoxetane

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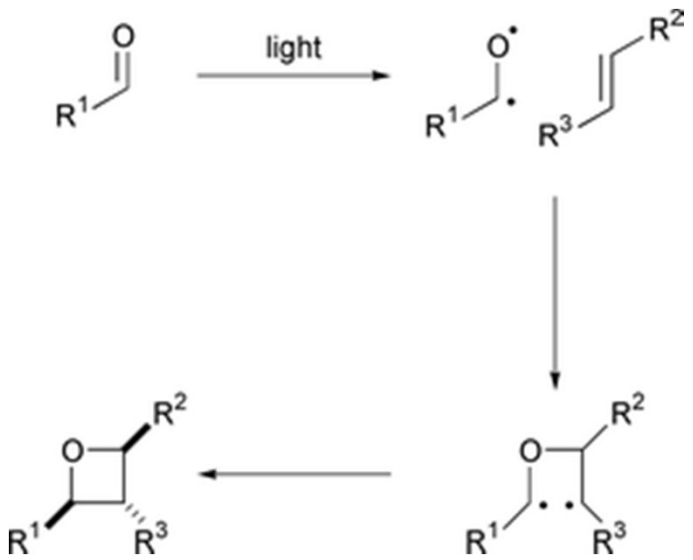
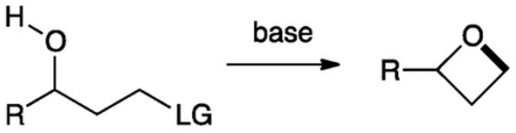
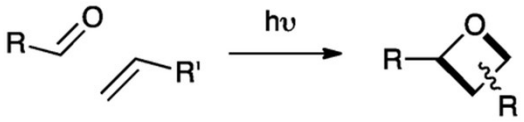


Williamson etherification
C–O formation

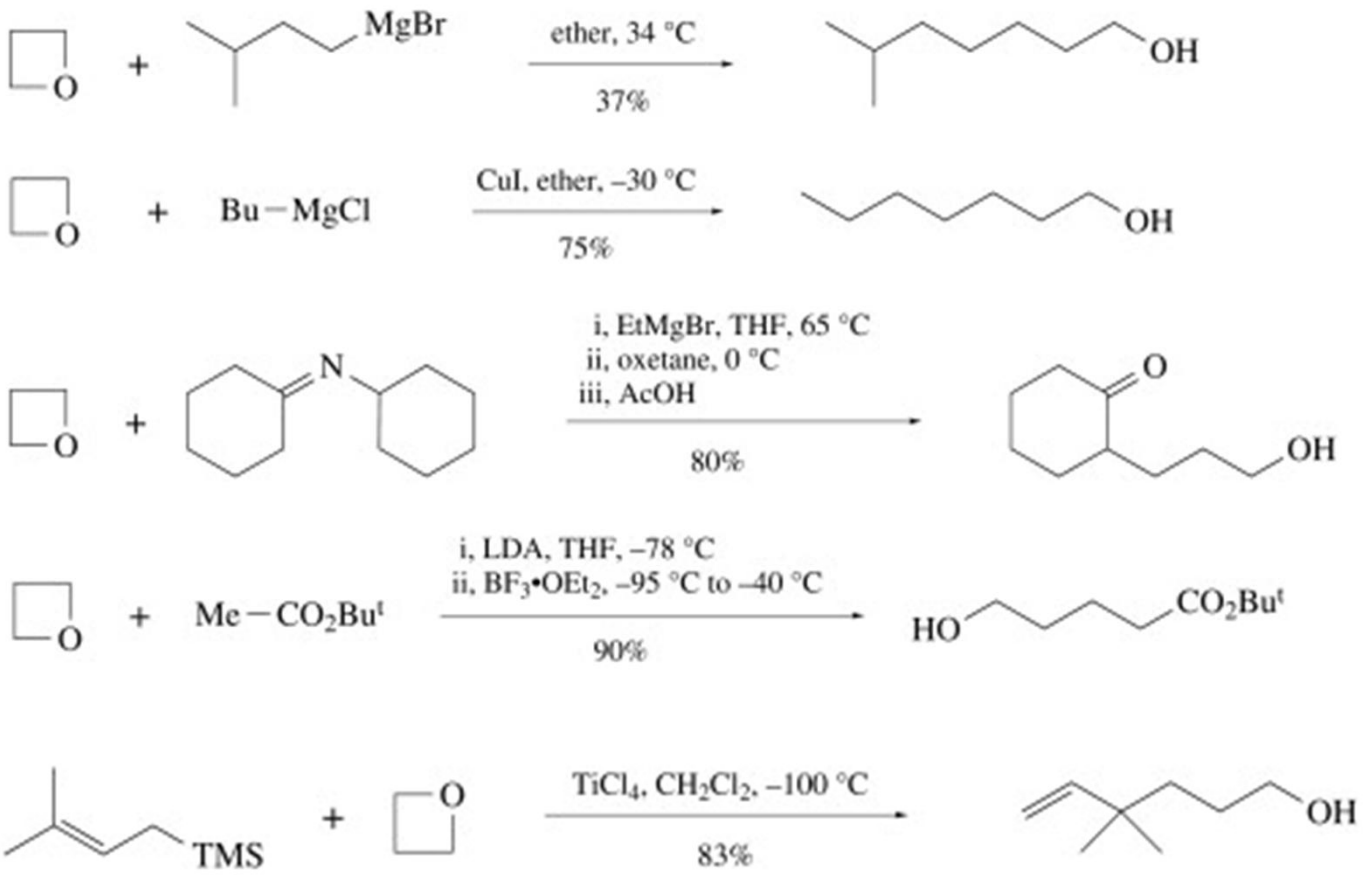


Paterno-Buchi photchemical 2+2
C–C and C–O formation



This work
C–C bond formation

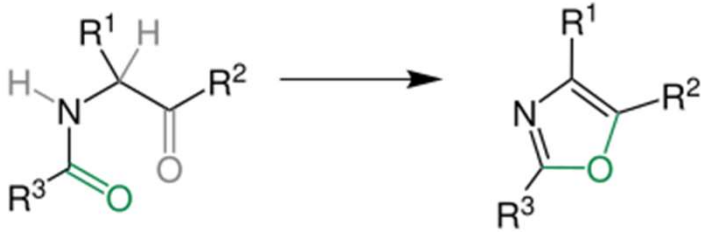
R = anion stabilising group



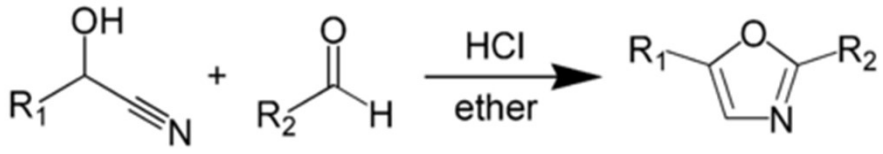
Oxazole

Oxazole is the parent compound for a vast class of heterocyclic aromatic organic compounds. These are azoles with an oxygen and a nitrogen separated by one carbon.[2] Oxazoles are aromatic compounds but less so than the thiazoles. Oxazole is a weak base.

The **Robinson–Gabriel synthesis** is an organic reaction in which a 2-acylamino-ketone reacts intramolecularly followed by a dehydration to give an oxazole.



The **Fischer oxazole synthesis** is a chemical synthesis of an oxazole from a cyanohydrin and an aldehyde in the presence of anhydrous hydrochloric acid.



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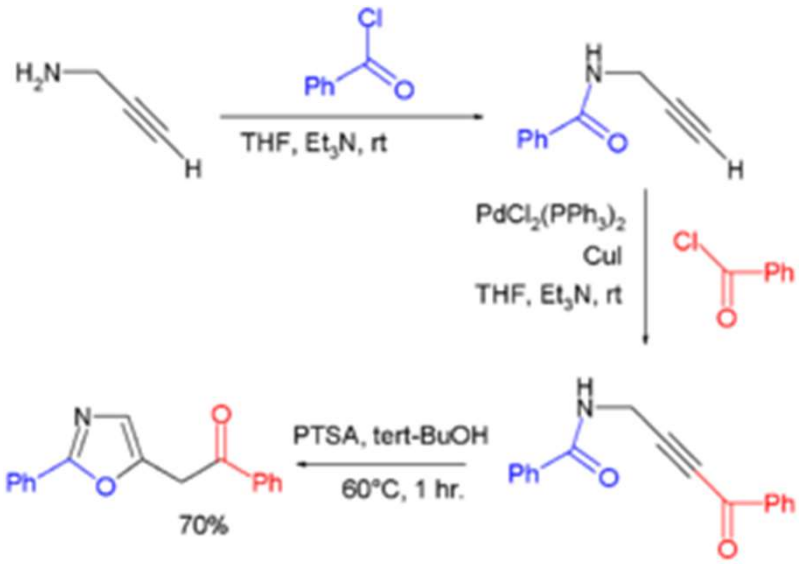

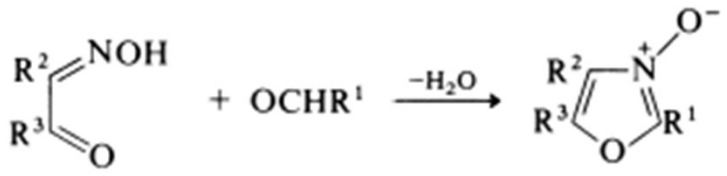

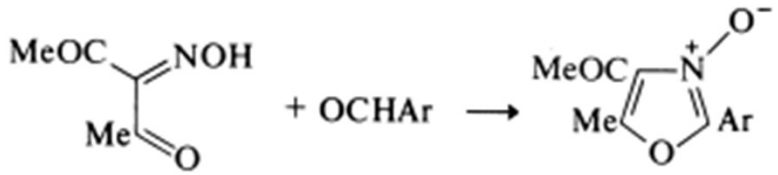

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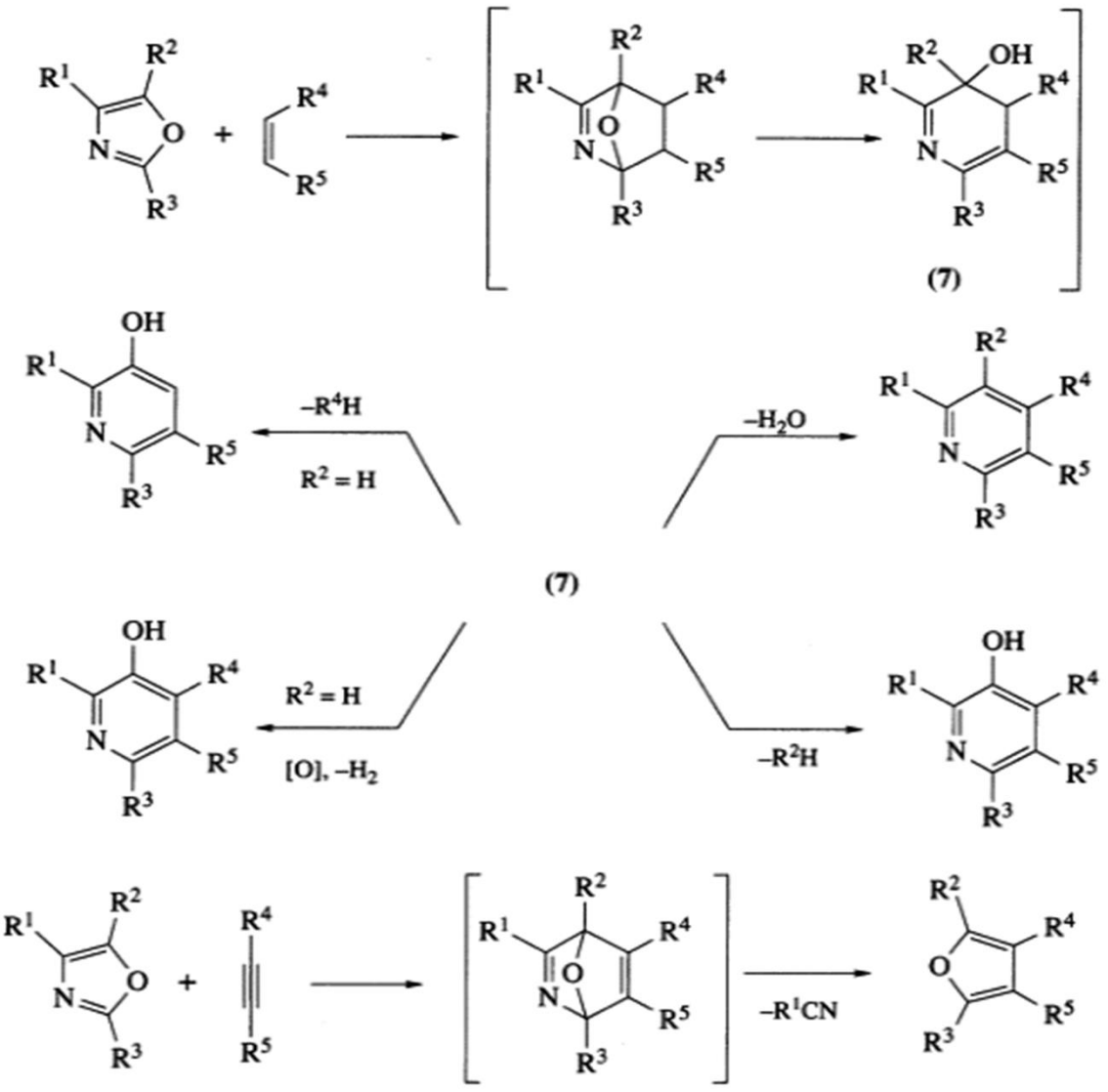

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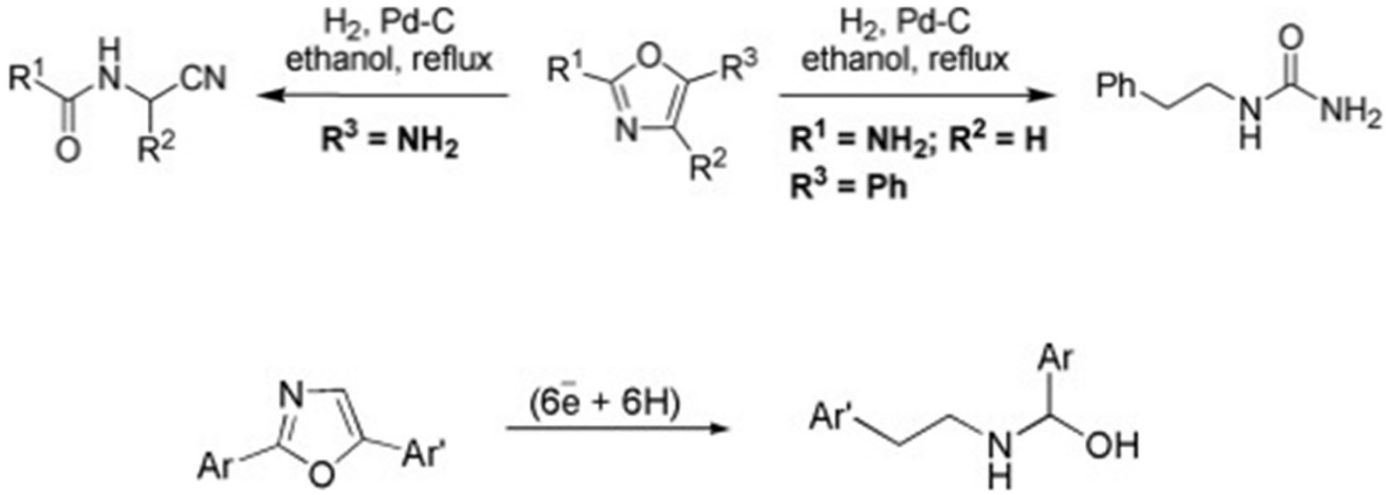

Imidazole

Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid, soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms. Many natural products, especially alkaloids, contain the imidazole ring.

When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature.

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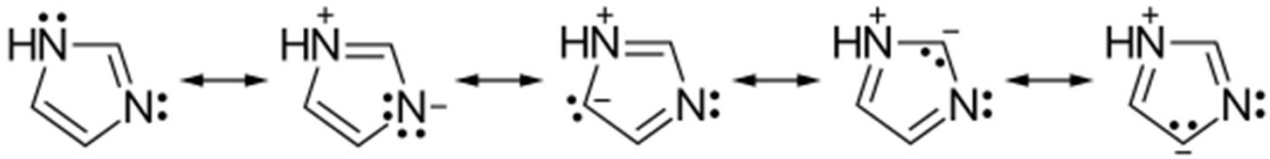
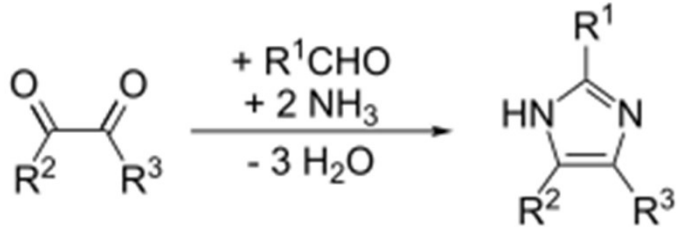
Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D. The compound is classified as aromatic due to the presence of a planar ring containing 6 π-electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring). Some resonance structures of imidazole are shown below:



Imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair

Glyoxal, formaldehyde, and ammonia condense to form imidazole



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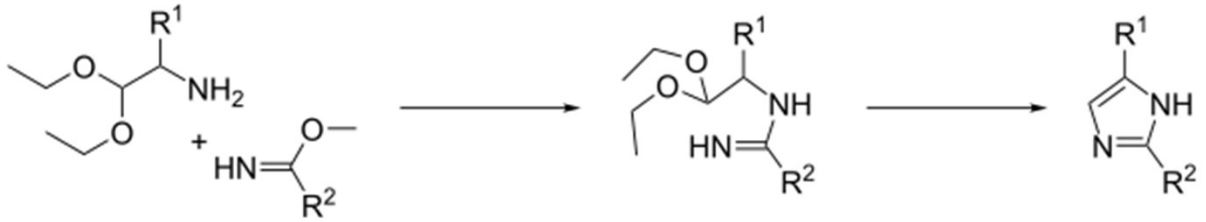
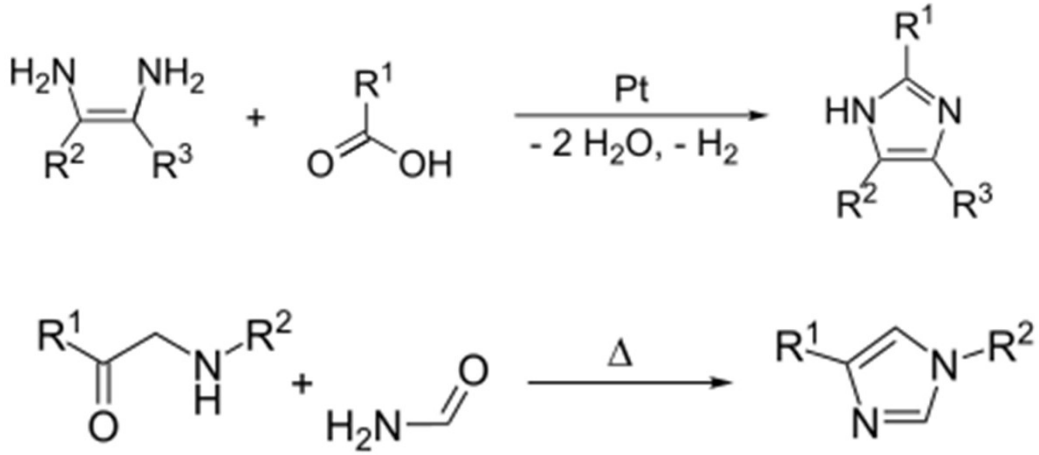
The (1,5) or (3,4) bond can be formed by the reaction of an imidate and an α-aminoaldehyde or α-aminoacetal. The example below applies to imidazole when $R_1 = R_2$ = hydrogen.



The (1,2) and (2,3) bonds can be formed by treating a 1,2-diaminoalkane, at high temperatures, with an alcohol, aldehyde, or carboxylic acid. A dehydrogenating catalyst, such as platinum on alumina, is required.



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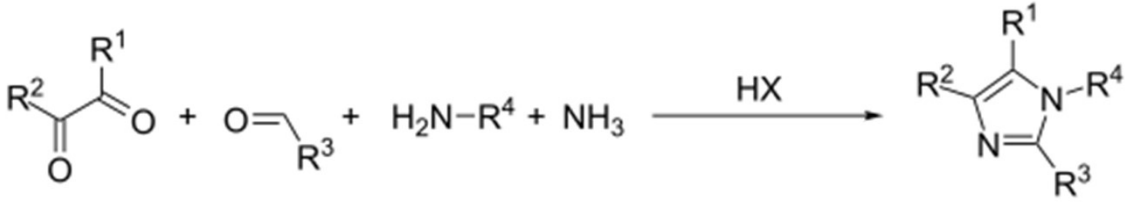
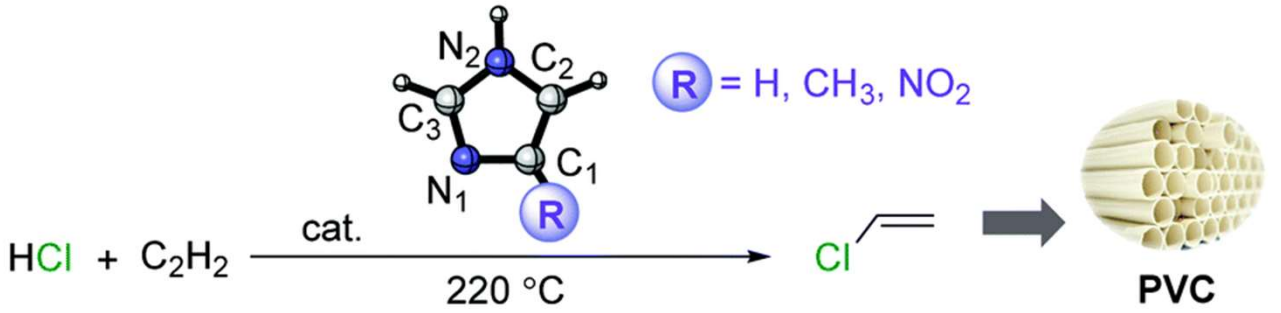
An adaptation of the Debus method, it is called the Debus-Radziszewski imidazole synthesis. The starting materials are substituted glyoxal, aldehyde, amine, and ammonia or an ammonium salt.

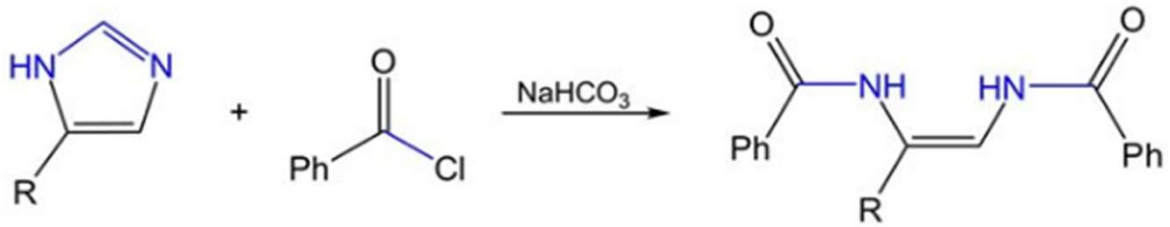


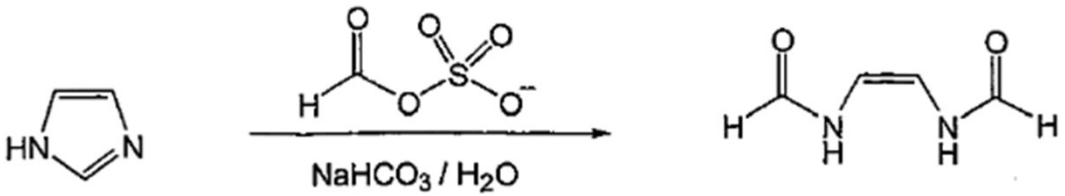
Imidazole is a base and an excellent nucleophile. It reacts at the NH nitrogen, attacking alkylating and acylating compounds. It is not particularly susceptible to electrophilic attacks at the carbon atoms, and most of these reactions are substitutions that keep the aromaticity intact.

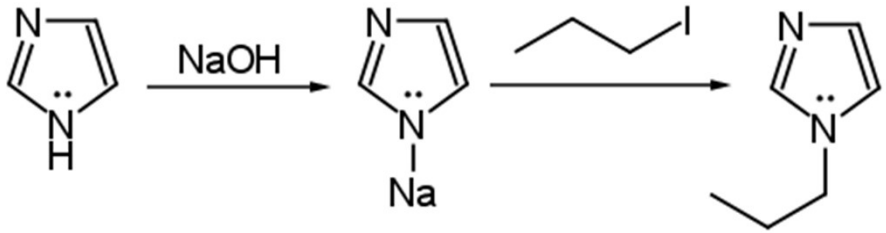
The imidazole-catalyzed direct hydrochlorination of acetylene with HCl

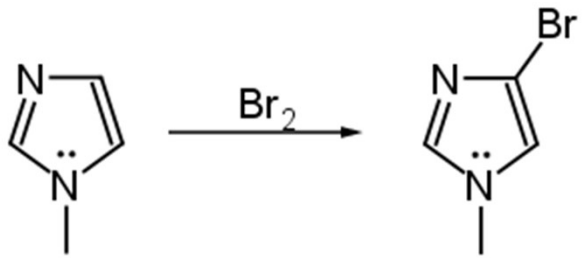


A combined experimental and computational study









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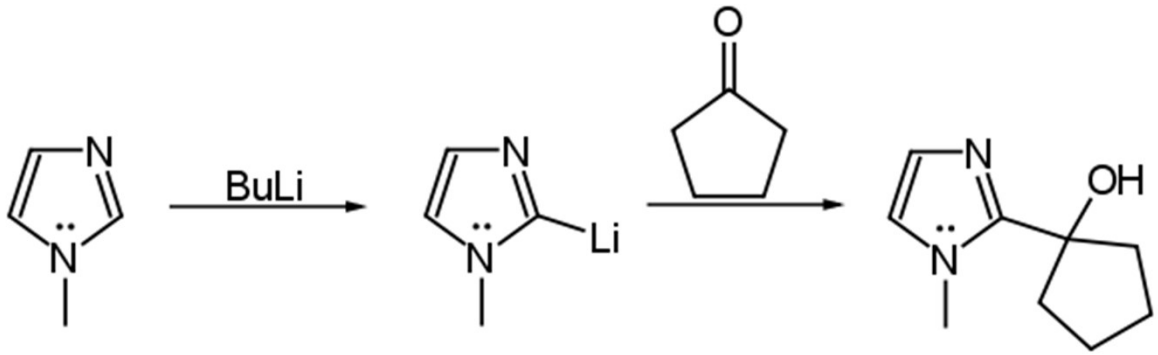
N
N
BuLi
N
N
Li
O
N
N
OH

Imidazole

Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid. Soluble in water. Giving a mildly alkaline solution.

In chemistry, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms.

Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-C_3N_2 ring but feature varied substituents.

This ring system is present in important biological building blocks, such as histidine and the related hormone histamine.

Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.

When fused to a pyrimidine ring, it forms a purine, which is the most widely occurring nitrogen-containing heterocycle in nature.

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Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom.

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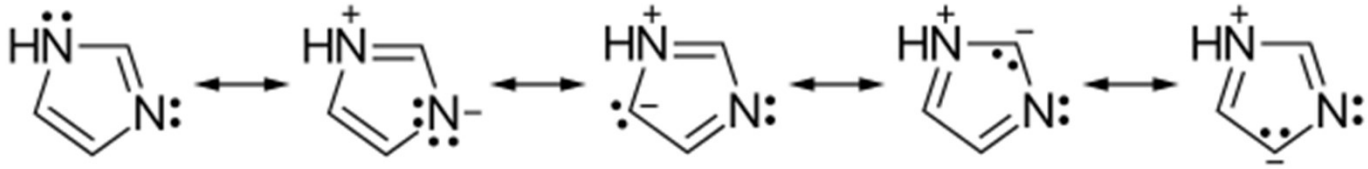
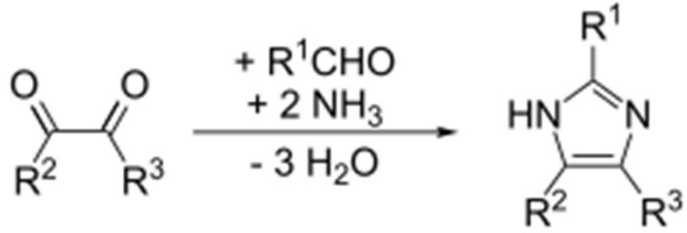
The compound is classified as aromatic due to the presence of a planar ring containing 6 π-electrons. Some resonance structures of imidazole are shown below:



Imidazole is amphoteric. That is, it can function as both an acid and as a base.

Glyoxal, formaldehyde, and ammonia condense to form imidazole



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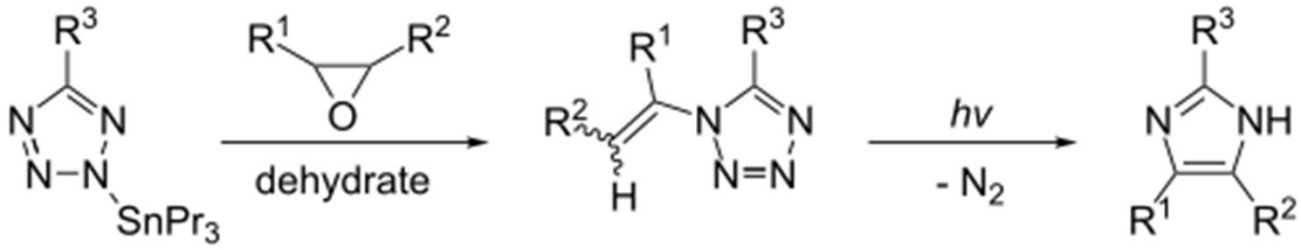
Imidazole can be synthesized by the photolysis of 1-vinyltetrazole.



Imidazole is incorporated into many important biological compounds. The most pervasive is the amino acid histidine, which has an imidazole side-chain.

Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin.

Imidazole-based histidine compounds play a very important role in intracellular buffering.

One of the applications of imidazole is in the purification of His-tagged proteins in immobilised metal affinity chromatography (IMAC).

The substituted imidazole derivatives are valuable in treatment of many systemic fungal infections.

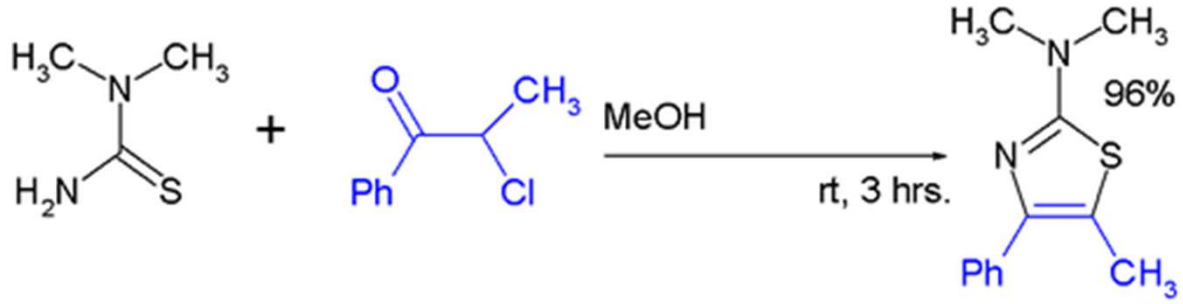
Thiazole

Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives.

Thiazole itself is a pale yellow liquid with a pyridine-like odor and the molecular formula C_3H_3NS. The thiazole ring is notable as a component of the vitamin thiamine (B_1).

Thiazoles are members of the azoles. Thiazoles are structurally similar to imidazoles, with the thiazole sulfur replaced by nitrogen.

A reaction between haloketones and thioamides



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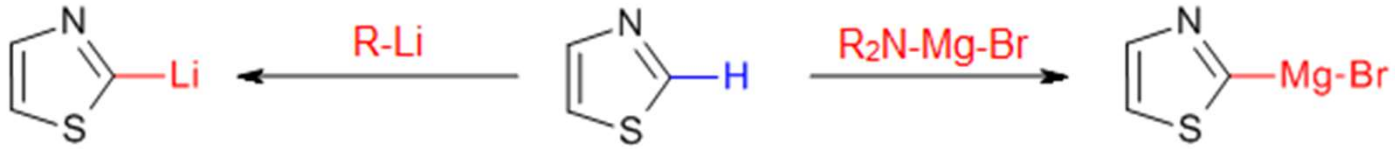
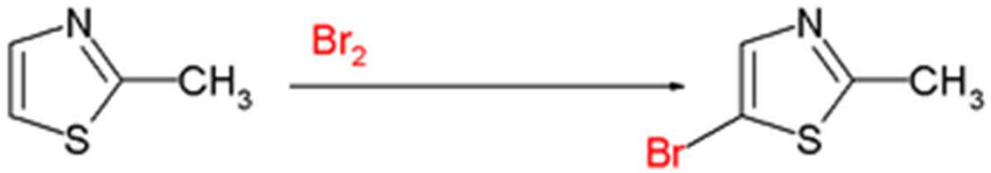
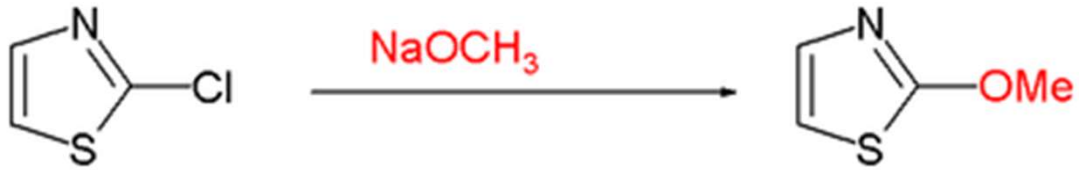
Deprotonation at C2



Electrophilic aromatic substitution at C5



Nucleophilic aromatic substitution



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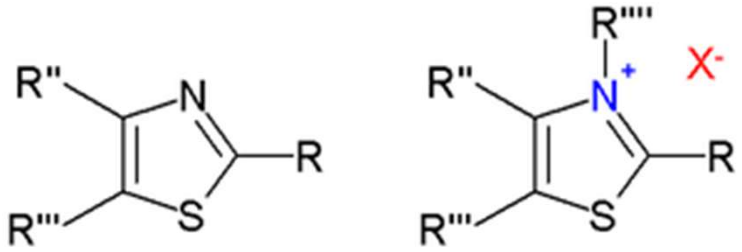
Alkylation of thiazoles at nitrogen forms a thiazolium cation.

Thiazolium salts are catalysts in the Stetter reaction and the Benzoin condensation.



Biosynthesis routes lead to the thiazole ring as required for the formation of thiamine.

Sulfur of the thiazole is derived from cysteine. In anaerobic bacteria, the CN group is derived from dehydroglycine.

Isoxazole

Isoxazole is an azole with an oxygen atom next to the nitrogen. It is also the class of compounds containing this ring.

Isoxazolyl is the univalent radical derived from isoxazole.

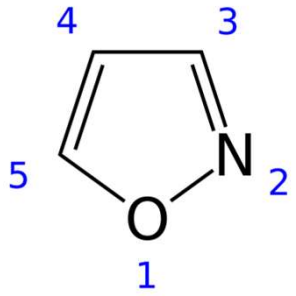
Isoxazole rings are found in some natural products, such as ibotenic acid and muscimol.

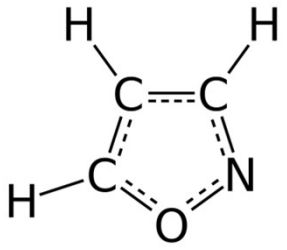
Isoxazoles also form the basis for a number of drugs, including the COX-2 inhibitor valdecoxib (Bextra) and a neurotransmitter agonist AMPA.

A derivative, furoxan, is a nitric oxide donor. An isoxazolyl group is found in many beta-lactamase-resistant antibiotics, such as cloxacillin, dicloxacillin and flucloxacillin.

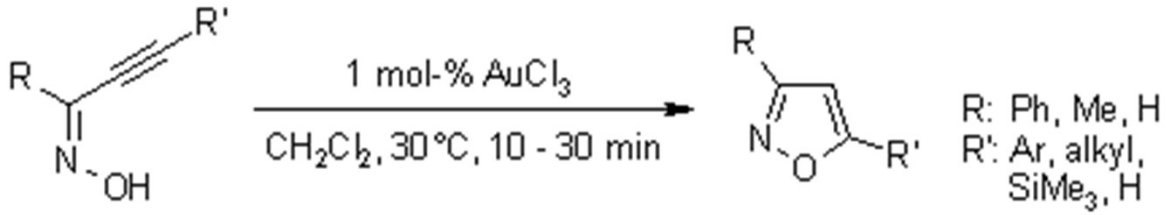
Leflunomide is an isoxazole-derivative drug. Examples of AAS containing the isoxazole ring include danazol and androisoxazole.

A number of pesticides are isoxazoles.

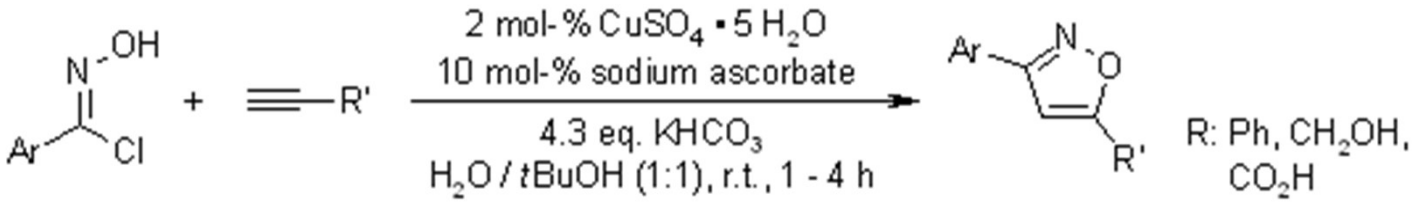




$AuCl_3$-catalyzed cycloisomerization of α,β-acetylenic oximes leads to substituted isoxazoles



Cycloadditions of copper(I) acetylides to azides and nitrile oxides provide ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles,



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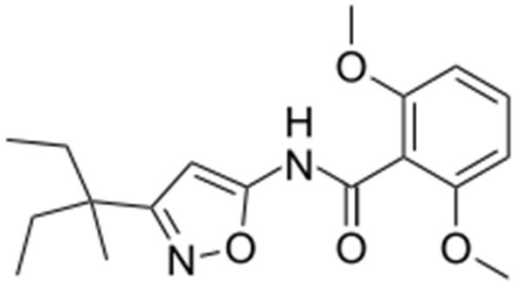

Isoxaben is an example of an isoxazole used as a herbicide.

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Pyrazole

Pyrazole is an organic compound with the formula $C_3H_3N_2H$.

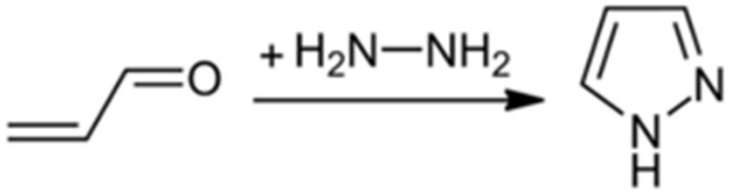
It is a heterocycle characterized by a 5-membered ring of three carbon atoms and two adjacent nitrogen atoms.

Pyrazole is a weak base.

Pyrazoles are also a class of compounds that have the ring C_3N_2 with adjacent nitrogen atoms.

Notable drugs containing a pyrazole ring are celecoxib (Celebrex) and the anabolic steroid stanozolol.

Pyrazoles are synthesized by the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation:



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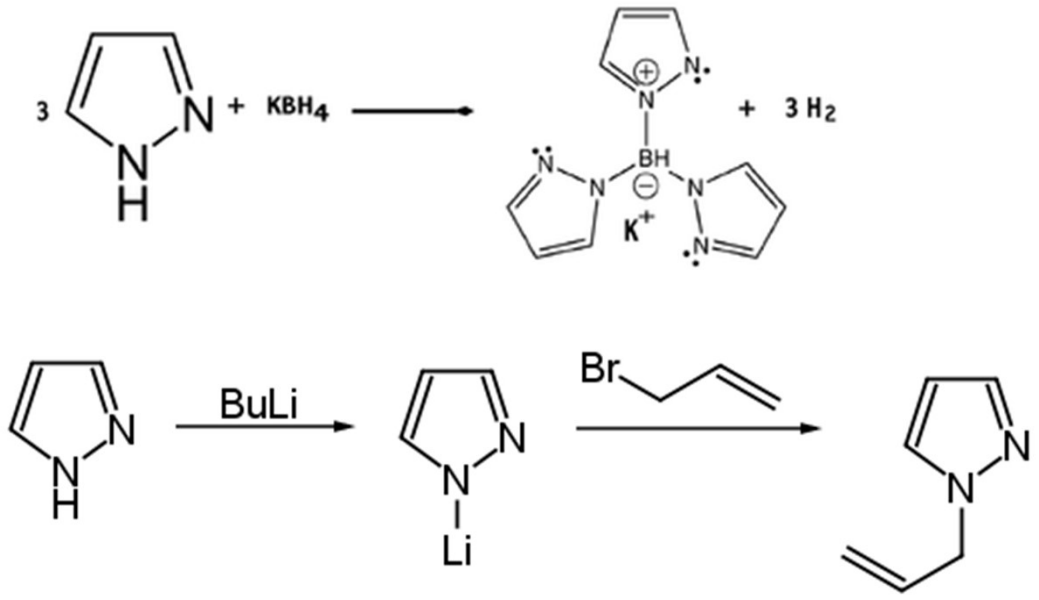
Substituted pyrazoles are prepared by condensation of 1,3-diketones with hydrazine (Knorr-type reactions).

$$CH_3C(O)CH_2C(O)CH_3 + N_2H_4 \rightarrow (CH_3)_2C_3HN_2H + 2\,H_2O$$

Pyrazoles react with potassium borohydride to form a class of ligands known as scorpionate. Pyrazole itself reacts with potassium borohydride at high temperatures (~200 °C) to form a tridentate ligand known as Tp ligand:



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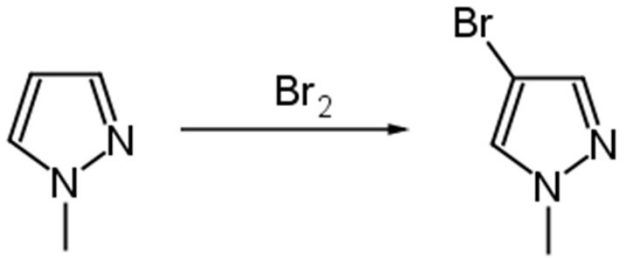
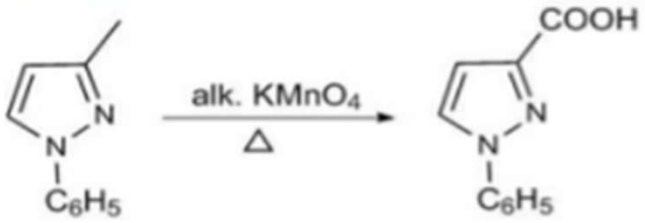
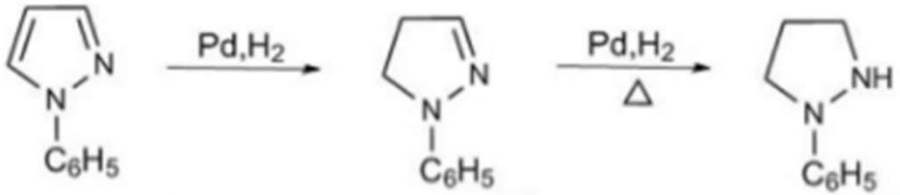


Oxidation



Reduction



1-phenylpyrazole

1-phenyl-4,5-dihydropyrazole

1-phenylpyrazolidine

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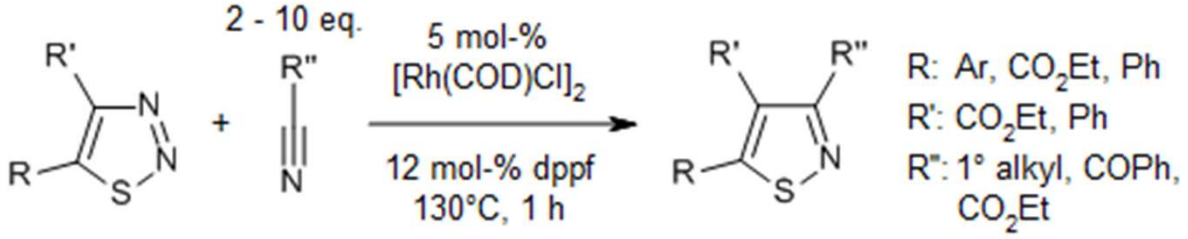
Isothiazole

Isothiazole or **1,2-thiazole**, is a type of organic compound containing a five-membered aromatic ring that consists of three carbon atoms, one nitrogen atom, and one sulfur atom.

Isothiazole is a member of a class of compounds known as azoles. In contrast to the isomeric thiazole, the two heteroatoms are in adjacent positions.

The ring structure of isothiazole is incorporated into larger compounds with biological activity such as the pharmaceutical drugs ziprasidone and perospirone.

A Rh-catalyzed transannulation of 1,2,3-thiadiazoles with alkyl, aryl, and heteroaryl nitriles provides a wide variety of isothiazoles via an α-thiavinyl Rh-carbenoid intermediate.



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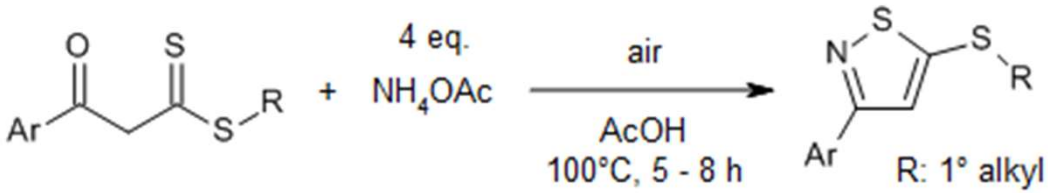
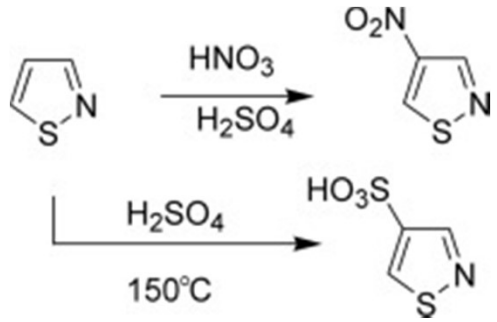
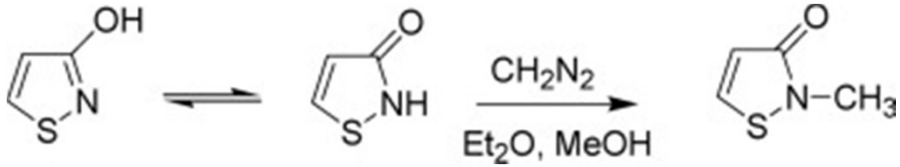
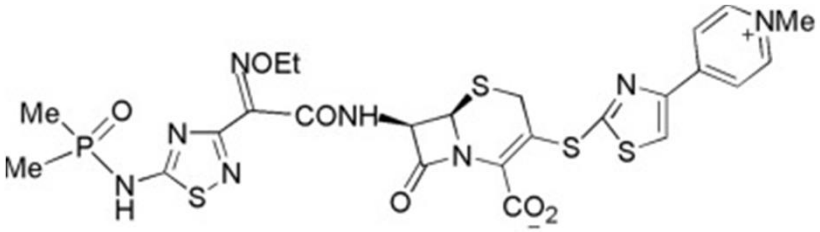
synthesis of 3,5-disubstituted/annulated isothiazoles from β-ketodithioesters/β-ketothioamides and NH_4OAc via C=O/C=S bond functionalization under metal- and catalyst-free conditions.

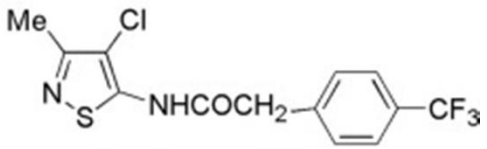




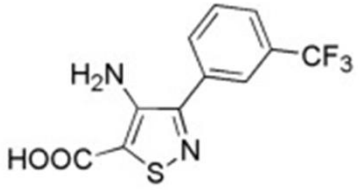




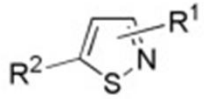
Cephalosporin (5th generation)
(Antibacterial)



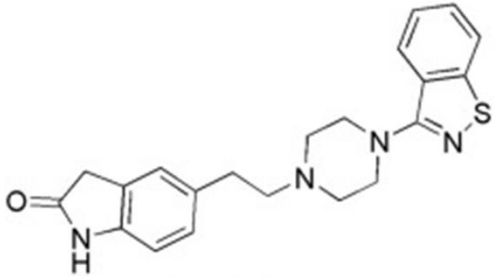
Used as pesticides



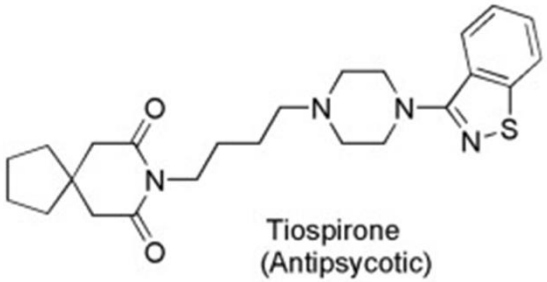
Serine proteases inhibitor



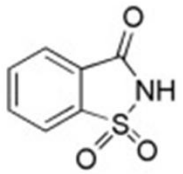
R^1= H, Alkyl, Aryl Cycloalkyl
R^2= Substituted pyrrolidinyl
Antialzheimer



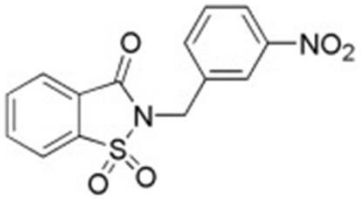
Ziprasidone
(Antipsychotic)



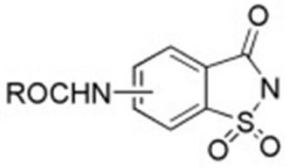
Tiospirone
(Antipsycotic)



Saccharine



Antitumor



Antitumor

R=Me,Aryl

Triazole

A triazole refers to any of the heterocyclic compounds with molecular formula $C_2H_3N_3$, having a five-membered ring of two carbon atoms and three nitrogen atoms.

There are two sets of isomers that differ in the relative positions of the three nitrogen atoms.

Each of these has two tautomers that differ by which nitrogen has a hydrogen bonded to it.

The triazole antifungal drugs include fluconazole, isavuconazole, itraconazole, voriconazole, pramiconazole, ravuconazole, and posaconazole.

The triazole plant protection fungicides include epoxiconazole, triadimenol [de], propiconazole, prothioconazole, metconazole, cyproconazole, tebuconazole, flusilazole and paclobutrazol.
Paclobutrazol, uniconazole, flutriafol [de], and triadimefon are used as plant growth retardants.

Brassinazole is Brassinosteroid Biosynthesis Inhibitor.
Benzotriazole is used in chemical photography as a restrainer and fog suppressant.

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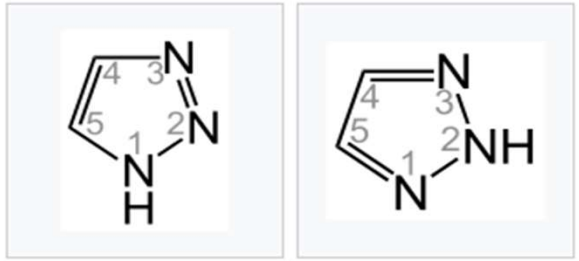
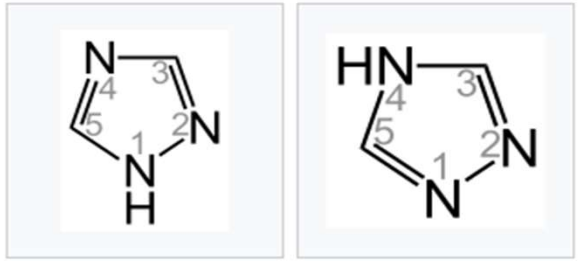
1,2,3-Triazole



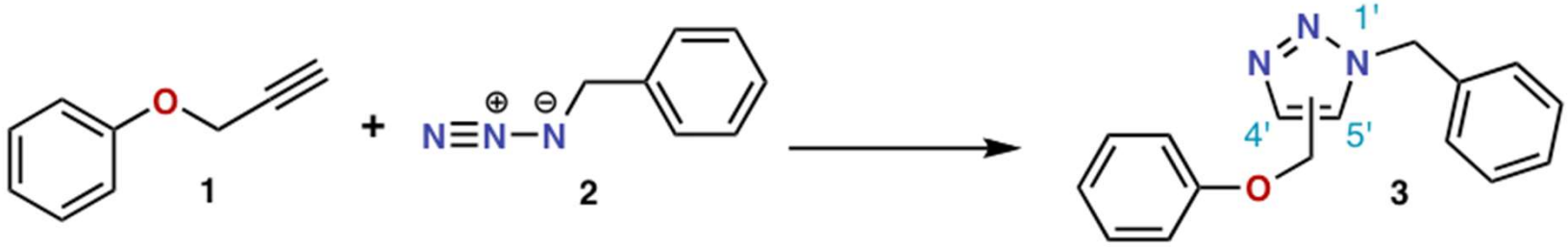
1*H*-1,2,3-Triazole 2*H*-1,2,3-Triazole

1,2,4-Triazole



1*H*-1,2,4-Triazole 4*H*-1,2,4-Triazole

The azide-alkyne Huisgen cycloaddition is a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a 1,2,3-triazole.



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The reaction has been widely used in bioorthogonal chemistry and in organic synthesis.

Triazoles are relatively stable functional groups and triazole linkages can be used in a variety of applications.

Due to spreading resistance of plant pathogens towards fungicides of the strobilurin class, control of fungi such as *Septoria tritici* or *Gibberella zeae* relies heavily on triazoles.

Food, like store bought potatoes, contain retardants such as triazole or tetcyclacis.

1,2,3-Triazole with water forms hydronium ions and triazolium anions.

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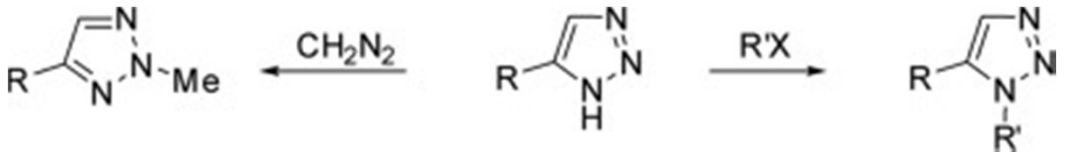
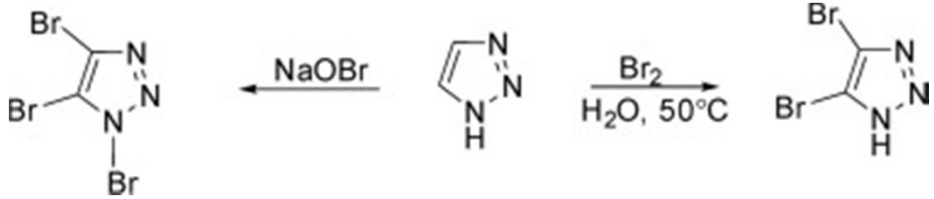
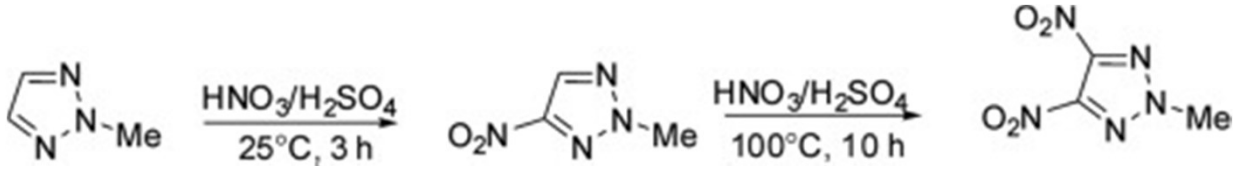
Alkylation of 1*H*-1,2,3-triazoles by alkyl halide and dimethyl sulfate usually gave 1-alkyl-1*H*-1,2,3-triazole



1,2,3-Triazole is easily brominated with bromine in water at 45°C and afforded 4,5-dibromo-1*H*-1,2,3-triazole, while bromination with NaOBr in acetic acid afforded 1,4,5-tribromo-1,2.3-triazole





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Pyrimidine

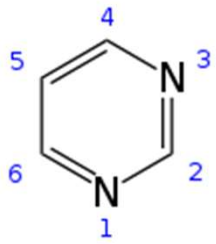
Pyrimidine is an aromatic heterocyclic organic compound similar to pyridine. One of the three diazines (six-membered heterocyclics with two nitrogen atoms in the ring), it has the nitrogen atoms at positions 1 and 3 in the ring.

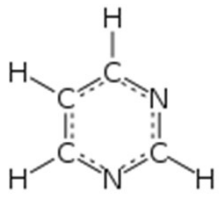
In nucleic acids, three types of nucleobases are pyrimidine derivatives: cytosine (C), thymine (T), and uracil (U).

Six-membered heterocycles can be described as π-deficient. These effects also decrease the basicity.

Because of the decreased basicity compared to pyridine, electrophilic substitution of pyrimidine is less facile.

Pyrimidine is also found in meteorites, but scientists still do not know its origin. Pyrimidine also photolytically decomposes into uracil under ultraviolet light.





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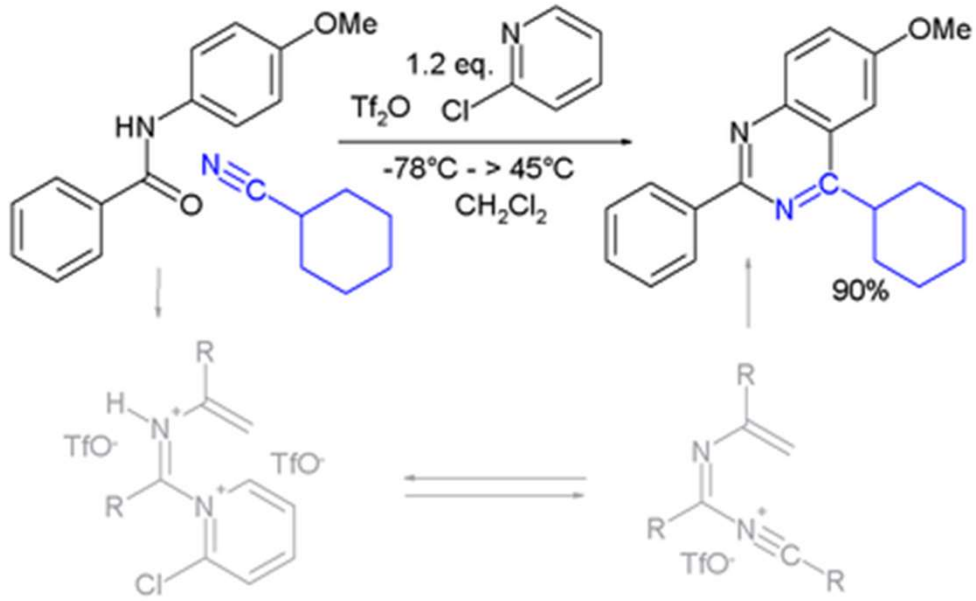
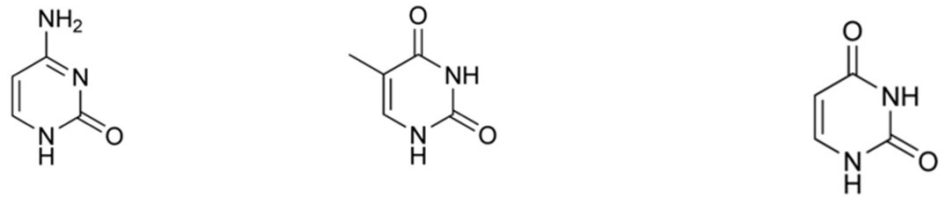
Reaction of *N*-vinyl and *N*-aryl amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluoromethanesulfonic anhydride.



Three nucleobases found in nucleic acids, cytosine (C), thymine (T), and uracil (U), are pyrimidine derivatives:



Free radical attack has been observed for pyrimidine and photochemical reactions have been observed for substituted pyrimidines.

Pyrimidine can be hydrogenated to give tetrahydropyrimidine.

Amination and hydroxylation has been observed for substituted pyrimidines.

Reduction in resonance stabilization of pyrimidines may lead to addition and ring cleavage reactions rather than substitutions.

Purine

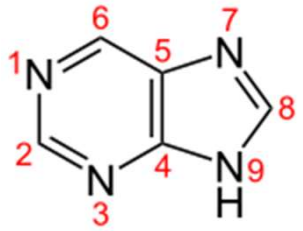
Purine is a heterocyclic aromatic organic compound that consists of two rings in their structure.

It is water-soluble. Purine also gives its name to the wider class of molecules, purines, which include substituted purines and their tautomers.

They are the most widely occurring nitrogen-containing heterocycles in nature.

Purines are found in high concentration in meat and meat products, especially internal organs such as liver and kidney. In general, plant-based diets are low in purines.

Examples of high-purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, meat extracts (e.g., Oxo, Bovril), herring, mackerel, scallops, game meats, beer (from the yeast) and gravy.



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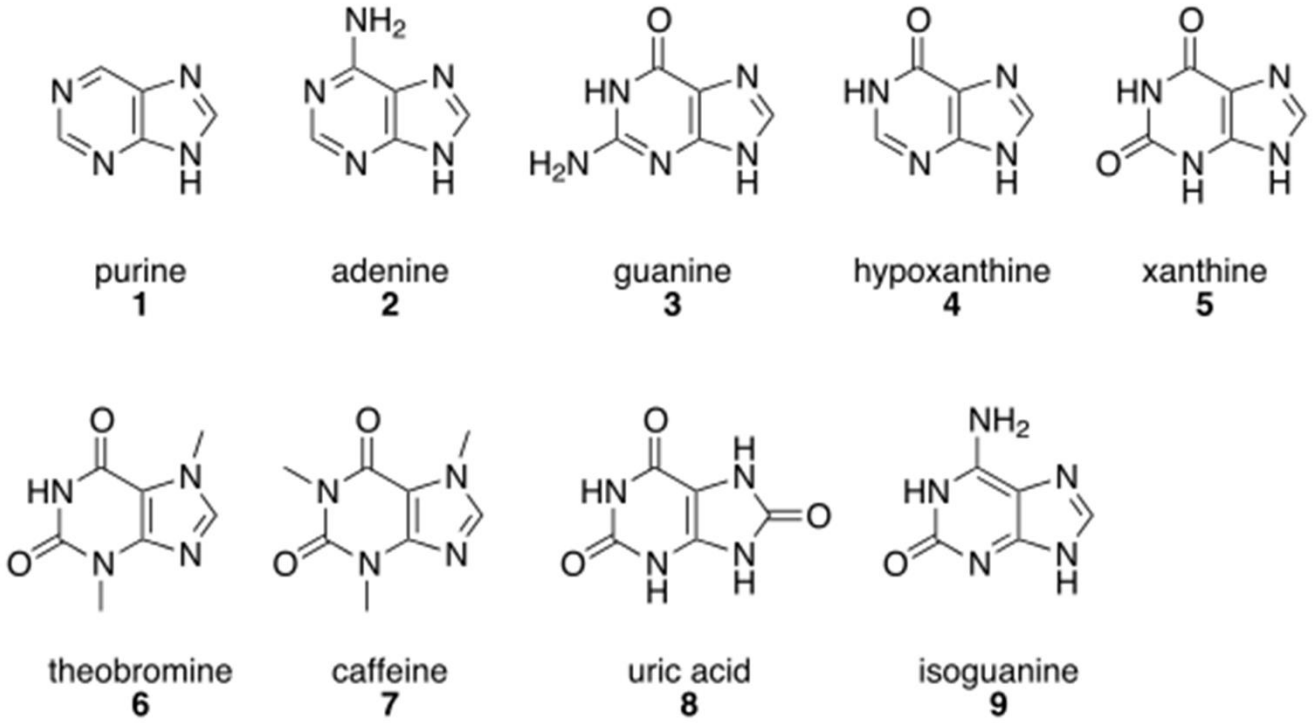
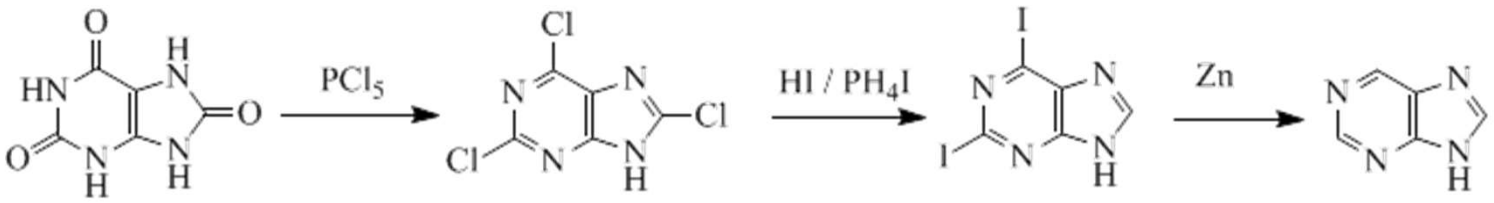
Purine is both a very weak acid (pK_a 2.39) and an even weaker base (pK_a 8.93).

If dissolved in pure water, the pH will be halfway between these two pKa values.

There are many naturally occurring purines.





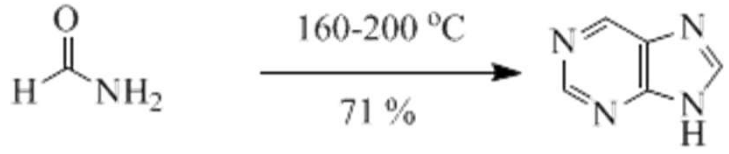
8
uric acid

10
2,6,8-trichloropurine

11
2,6-diiodopurine

1
purine

Purine is obtained in good yield when formamide is heated in an open vessel at 170 °C for 28 hours.



formamide

purine
1

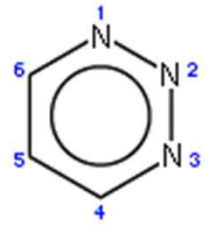
Aside from the crucial roles of purines (adenine and guanine) in DNA and RNA, purines are also significant components in a number of other important biomolecules, such as ATP, GTP, cyclic AMP, NADH, and coenzyme A.

Purine itself, has not been found in nature, but it can be produced by organic synthesis. They may also function directly as neurotransmitters, acting upon purinergic receptors. Adenosine activates adenosine receptors.

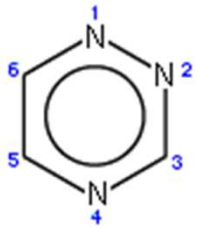
Triazines

Triazines are a class of nitrogen-containing heterocycles. The parent molecules' molecular formula is $C_3H_3N_3$. They exist in three isomeric forms, 1,3,5-triazines being common.

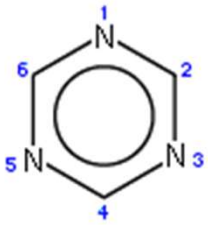
The three isomers of triazine are distinguished by the positions of their nitrogen atoms, and are referred to as 1,2,3-triazine, 1,2,4-triazine, and 1,3,5-triazine.



1,2,3-triazine



1,2,4-triazine



1,3,5-triazine
or
s-triazine

The triazines have planar six-membered benzene-like ring but with three carbons replaced by nitrogens.

A well known triazine is melamine (2,4,6-triamino-1,3,5-triazine). With three amino substituents, melamine is a precursor to commercial resins.

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The more common 1,3,5-isomers are prepared by trimerization of nitrile and cyanide compounds, although more specialized methods are known.

The 1,2,3- and 1,2,4-Triazines are more specialized methods. The former family of triazines can be synthesized by thermal rearrangement of 2-azidocyclopropenes.

Also mainly of specialized interest, the 1,2,4-isomer is prepared from condensation of 1,2-dicarbonyl compounds with amidrazones. A classical synthesis is also the Bamberger triazine synthesis.

Although triazines are aromatic compounds, their resonance energy is much lower than in benzene.

Electrophilic aromatic substitution is difficult but nucleophilic aromatic substitution easier than typical chlorinated benzenes.

2,4,6-Trichloro-1,3,5-triazine is easily hydrolyzed to cyanuric acid by heating with water.

Cyanuric chloride assists in the amidation of carboxylic acids.

The 1,2,4-triazines can react with electron-rich dienophiles in an inverse electron demand Diels-Alder reaction.

This forms a bicyclic intermediate which normally then extrudes a molecule of nitrogen gas to form an aromatic ring again.

Triazines also have wide use in the oil and gas and petroleum processing industries as a non-regenerating sulfide removal agent.

They are applied to fluid streams to remove hydrogen sulfide gas and mercaptan species, which can decrease the quality of the processed hydrocarbon and be harmful to pipeline and facility infrastructure if not removed.

Pyridazine

Pyridazine is a heterocyclic organic compound with the molecular formula $(CH)_4N_2$.

Six-membered ring with two adjacent nitrogen atoms, and is aromatic. It is a colorless liquid with a boiling point of 208 °C.

It is isomeric with two other $(CH)_4N_2$ rings, pyrimidine and pyrazine.

Pyridazines are rare in nature.

The pyridazine structure is a popular pharmacophore is found within a number of herbicides such as credazine, pyridafol and pyridate.

It is also found in several drugs such as cefozopran, cadralazine, minaprine, pipofezine, and hydralazine.

Condensation of phenylhydrazine and levulinic acid gives Pyridazine.

And also the condensation of 1,4-diketones or 4-ketoacids with hydrazines gives Pyridazine.

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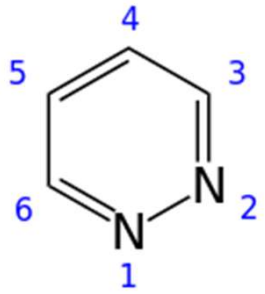
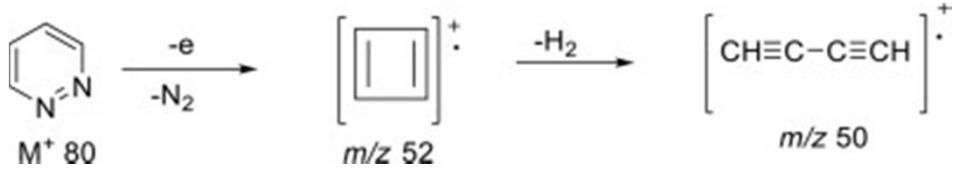
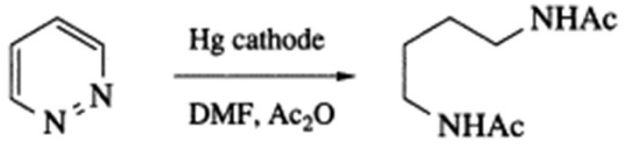
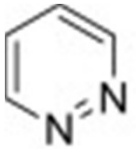


Pyridazine being a 6π heteroaromatic diazine is electron deficient due to the inductive effect of nitrogen atoms that induces a partial positive charge on carbon atoms.

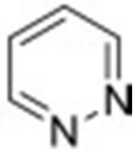
The π electron density in pyridazine in comparison to pyridine is consistent with the observed lower reactivity toward electrophiles compared to nucleophiles.







(I)



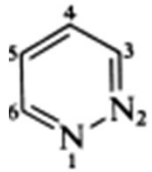
(II)

Pyridazine has been considered to be a resonance hybrid of two Kekulé structures (I and II).

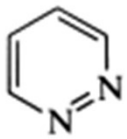
Both the structures are nonequivalent.

However, structure II makes a greater contribution to the resonance hybrid.

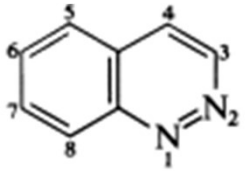
Pyridazine and its benzo analogs cinnoline (1,2-diazanaphthalene) or benzo[*c*]pyridazine and phthalazine (benzo[*d*]pyridazine)



(1a)



(1b)



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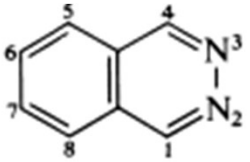
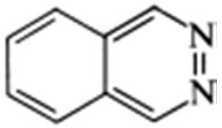


(3a)



(3b)

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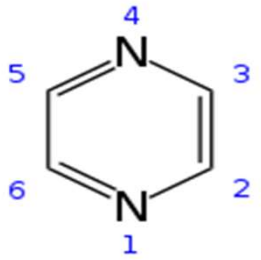
Pyrazine

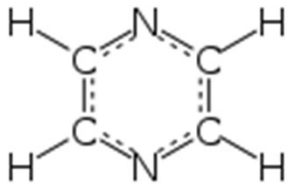
Pyrazine is a heterocyclic aromatic organic compound with the chemical formula $C_4H_4N_2$.

It is a symmetrical molecule with point group D_{2h}.

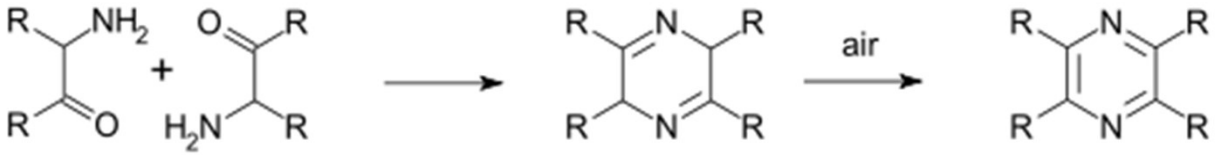
Pyrazine is less basic than pyridine, pyridazine and pyrimidine.

Pyrazine and a variety of alkylpyrazines are flavor and aroma compounds found in baked and roasted goods.





Gutknecht pyrazine synthesis



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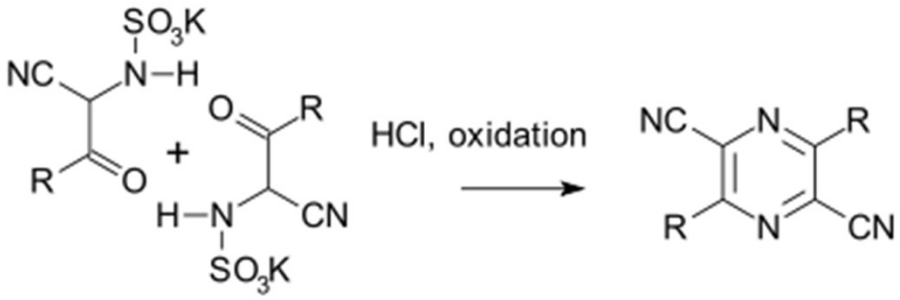
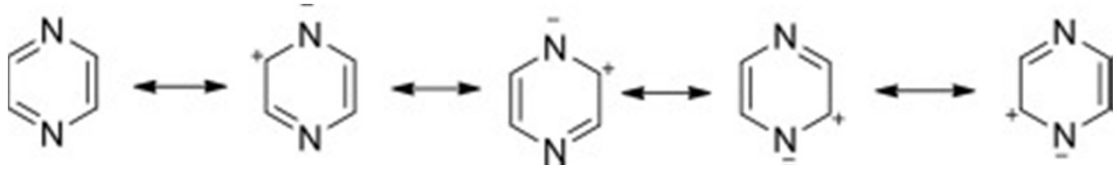
Gastaldi synthesis



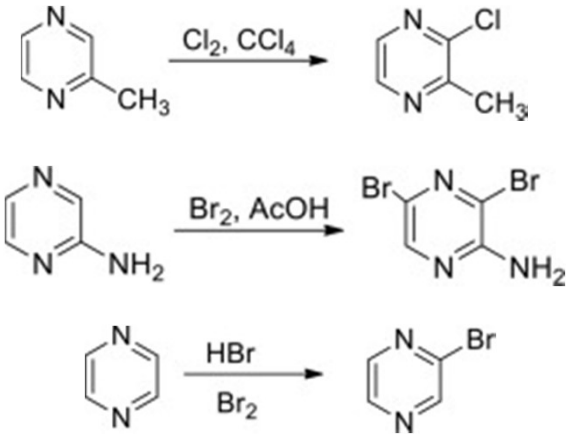
Pyrazine being an aromatic compound can be represented as a resonance hybrid of a number of canonical structures.



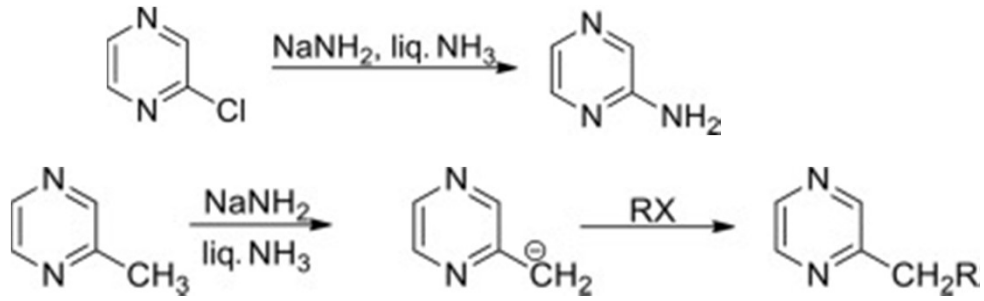
From the canonical structures it can be seen that in pyrazine there are electron deficiencies at 2, 3, 5, and 6.

Thus these positions can be attacked by nucleophilic reagents.

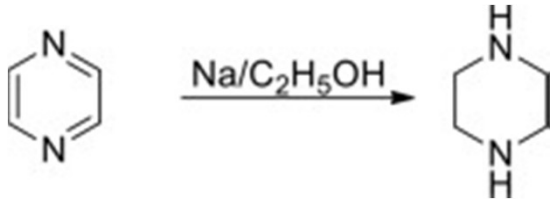
Electrophilic substitution reactions



Nucleophilic substitution reactions



Reduction of pyrazine with sodium and ethanol give piperazine.



P16CH31 / ORGANIC CHEMISTRY II

Unit-V: Natural Products

Terpenoids

The terpenoids, sometimes called isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from the 5-carbon compound isoprene, and the isoprene polymers called terpenes.

About 60% of known natural products are terpenoids.

Plant terpenoids are used for their aromatic qualities and play a role in traditional herbal remedies. Terpenoids contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, the yellow color in sunflowers, and the red color in tomatoes.

Well-known terpenoids include citral, menthol, camphor, salvinorin A in the plant *Salvia divinorum*, the cannabinoids found in cannabis, ginkgolide and bilobalide found in *Ginkgo biloba*, and the curcuminoids found in turmeric and mustard seed.

The Salkowski test (5 ml extract mixed with 2 ml of chloroform, and 3 ml of con. H_2SO_4 are carefully added to form a layer. A reddish brown coloration of the interface may formed to show positive results for the presence of terpenoids) can be used to identify the presence of terpenoids.

The **biosynthesis of (−)-menthol** takes place in the secretory gland cells of the peppermint plant. Geranyl diphosphate synthase (GPPS), first catalyzes the reaction of IPP (Isopentyl Pyrophosphate) and DMAPP into geranyl diphosphate.

Next (−)-limonene synthase (LS) catalyzes the cyclization of geranyl diphosphate to (−)-limonene.

(−)-Limonene-3-hydroxylase (L3OH), using O_2 and NADPH, then catalyzes the allylic hydroxylation of (−)-limonene at the 3 position to (−)-trans-isopiperitenol.

(−)-*trans*-Isopiperitenol dehydrogenase (iPD) further oxidizes the hydroxyl group on the 3 position using NAD^+ to make (−)-isopiperitenone.

(−)-Isopiperitenone reductase (iPR) then reduces the double bond between carbons 1 and 2 using NADPH to form (+)-*cis*-isopulegone.

(+)-*cis*-Isopulegone isomerase (iPI) then isomerizes the remaining double bond to form (+)-pulegone.

(+)-Pulegone reductase (PR) then reduces this double bond using NADPH to form (−)-menthone.

(−)-Menthone reductase (MR) then reduces the carbonyl group using NADPH to form (−)-menthol.

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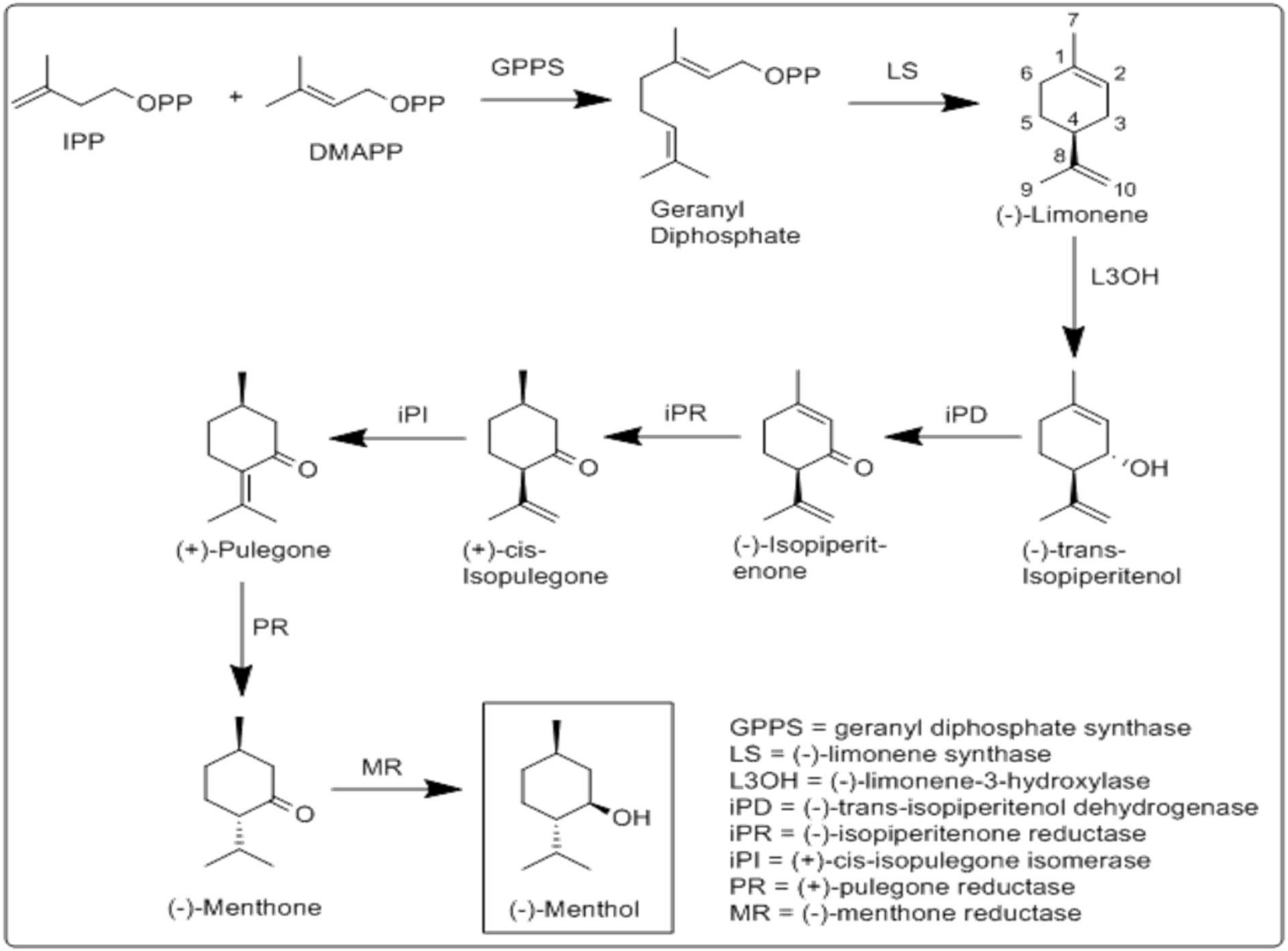

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Applications of Menthol

Menthol is included in many products, and for a variety of reasons. These include:
In nonprescription products for short-term relief of minor sore throat and minor mouth or throat irritation. Examples: lip balms and cough medicines.

As an antipruritic to reduce itching.

As a topical analgesic, it is used to relieve minor aches and pains, such as muscle cramps, sprains, headaches and similar conditions, alone or combined with chemicals such as camphor, eucalyptus oil or capsaicin. In Europe, it tends to appear as a gel or a cream, while in the U.S., patches and body sleeves are very frequently used. Examples: Tiger Balm, or IcyHot patches or knee/elbow sleeves.

As a penetration enhancer in transdermal drug delivery.
In decongestants for chest and sinuses (cream, patch or nose inhaler).. Examples: Vicks VapoRub, Mentholatum, VapoRem, Mentisan.
In certain medications used to treat sunburns, as it provides a cooling sensation (then often associated with aloe).

In aftershave products to relieve razor burn.

As a smoking tobacco additive in some cigarette brands, for flavor, and to reduce throat and sinus irritation caused by smoking. Menthol also increases nicotine receptor density, increasing the addictive potential of tobacco products.

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Commonly used in oral hygiene products and bad-breath remedies, such as mouthwash, toothpaste, mouth and tongue sprays, and more generally as a food flavor agent; such as in chewing gum and candy.

As a pesticide against tracheal mites of honey bees.
In perfumery, menthol is used to prepare menthyl esters to emphasize floral notes (especially rose).

In first aid products such as "mineral ice" to produce a cooling effect as a substitute for real ice in the absence of water or electricity (pouch, body patch/sleeve or cream).

In various patches ranging from fever-reducing patches applied to children's foreheads to "foot patches" to relieve numerous ailments (the latter being much more frequent and elaborate in Asia, especially Japan: some varieties use "functional protrusions", or small bumps to massage one's feet as well as soothing them and cooling them down).

In some beauty products such as hair conditioners, based on natural ingredients (e.g., St. ▪ Ives).

As an antispasmodic and smooth muscle relaxant in upper gastrointestinal endoscopy.

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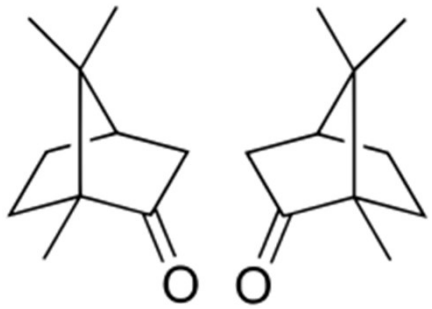
Camphor

Camphor is a waxy, flammable, transparent solid with a strong aroma. It is a terpenoid with the chemical formula $C_{10}H_{16}O$.

It is found in the wood of the camphor laurel (*Cinnamomum camphora*), a large evergreen tree found in East Asia, also of the unrelated *kapur tree* (*Dryobalanops sp.*), a tall timber tree from South East Asia.

It also occurs in some other related trees in the laurel family, notably *Ocotea usambarensis*. Rosemary leaves contain 0.05 to 0.5% camphor, while camphorweed contains some 5%.

A major source of camphor in Asia is camphor basil (the parent of African blue basil). Camphor can also be synthetically produced from oil of turpentine.



(+)- and (−)-camphor

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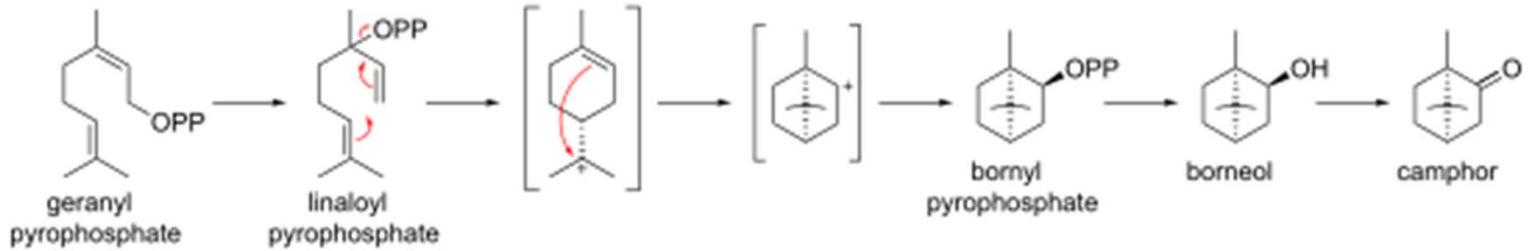
In biosynthesis, camphor is produced from geranyl pyrophosphate, via cyclisation of linaloyl pyrophosphate to bornyl pyrophosphate, followed by hydrolysis to borneol and oxidation to camphor.



Applications of Camphor

Cough. Camphor is FDA-approved as a chest rub in concentrations less than 11%.

Pain. Camphor is FDA-approved for use on the skin as a painkiller in concentrations of 3% to 11%. It is in many rub-on products for cold sores, insect stings and bites, minor burns, and hemorrhoids.

Skin itching or irritation. Camphor is FDA-approved for use on the skin to help itching or irritation in concentrations of 3% to 11%.

Osteoarthritis. A rub-on cream containing camphor, glucosamine sulfate, and chondroitin sulfate seems to reduce the severity of symptoms of osteoarthritis by about half.

Insect bite. Early research shows that applying camphor along with menthol and eucalyptus oil might help reduce the size of mosquito bites.

Low blood pressure after standing up. Early research suggests that taking a product containing camphor and hawthorn by mouth helps prevent drops in blood pressure upon standing. However, it is not clear if taking camphor alone provides the same benefits. Also, this product is not available in the US.

Total synthesis

The complete chemical synthesis of a complex molecule, often a natural product, from simple, commercially-available precursors.

It usually refers to a process not involving the aid of biological processes, which distinguishes it from semisynthesis.

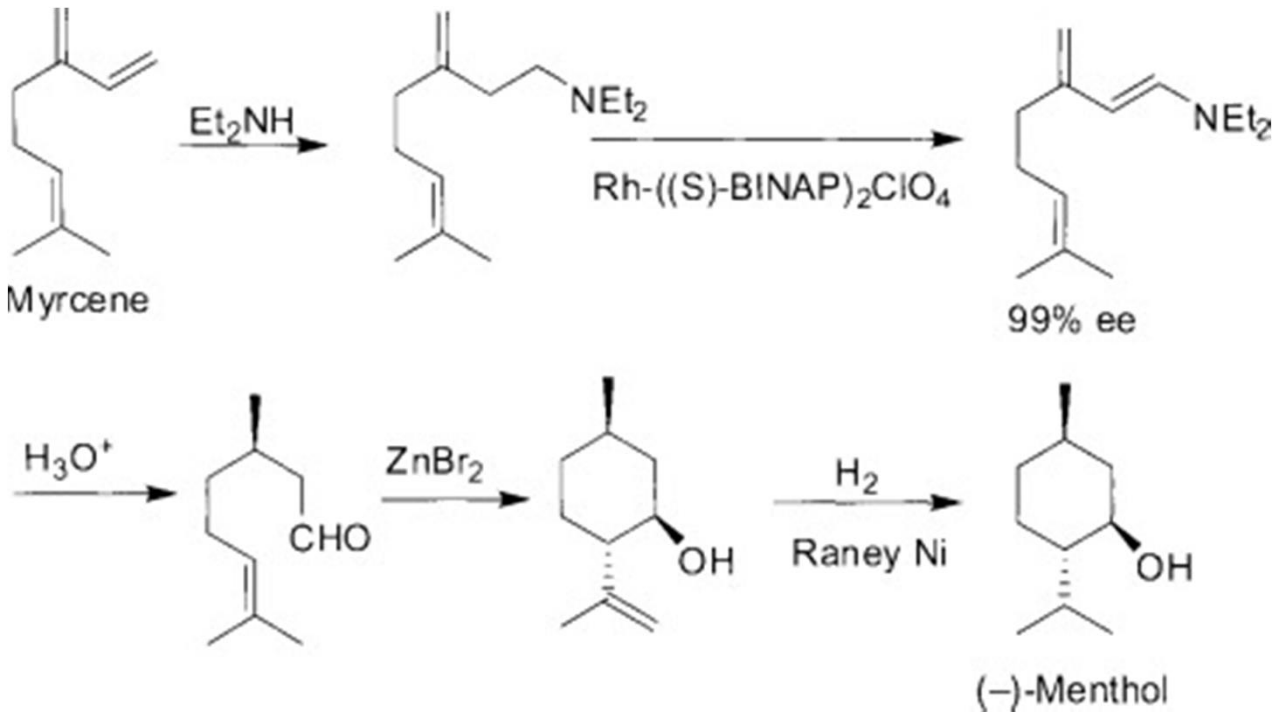
Takasago synthesis of menthol

Takasago developed the synthesis of (-)-menthol (in the 1980s) from myrcene, which is converted to diethylgeranylamine by the lithium-catalyzed addition of diethylamine.

This is then catalytically isomerized to the chiral 3R-citronella enamine with 96–99% enantiomeric excess.

Hydrolysis of this intermediate gave 3R-(+)-citronella a higher chiral purity than citronella from citronella oil.

This is the second major commercial route to (-)-menthol


Et2NH
NEt2
Rh-((S)-BINAP)2ClO4
NEt2
Myrcene
99% ee
H3O+
CHO
ZnBr2
OH
H2
Raney Ni
OH
(–)-Menthol

Corey's Synthesis of Longifolene

Longifolene is the common (or trivial) chemical name of a naturally occurring, oily liquid hydrocarbon found primarily in the high-boiling fraction of certain pine resins. The name is derived from that of a pine species from which the compound was isolated.

Chemically, longifolene is a tricyclic sesquiterpene. This molecule is chiral, and the enantiomer commonly found in pines.

Longifolene is also one of two most abundant aroma constituents of lapsang souchong tea, because the tea is smoked over pinewood fires.

Longifolene is used in organic synthesis for the preparation of dilongifolylborane (a chiral hydroborating agent).

Notable syntheses are by Corey the (+)-longifolene using an intramolecular Diels-Alder strategy.

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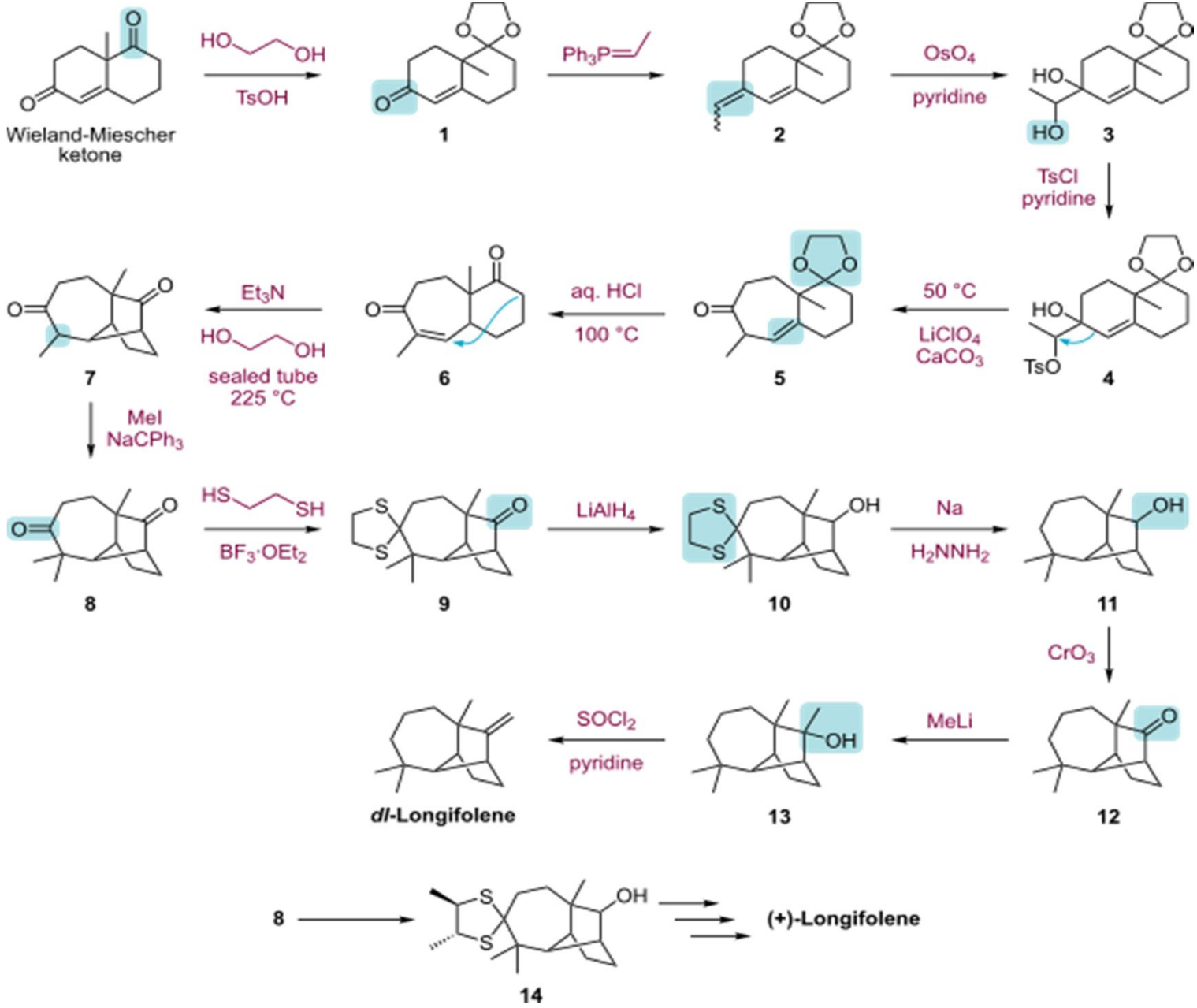

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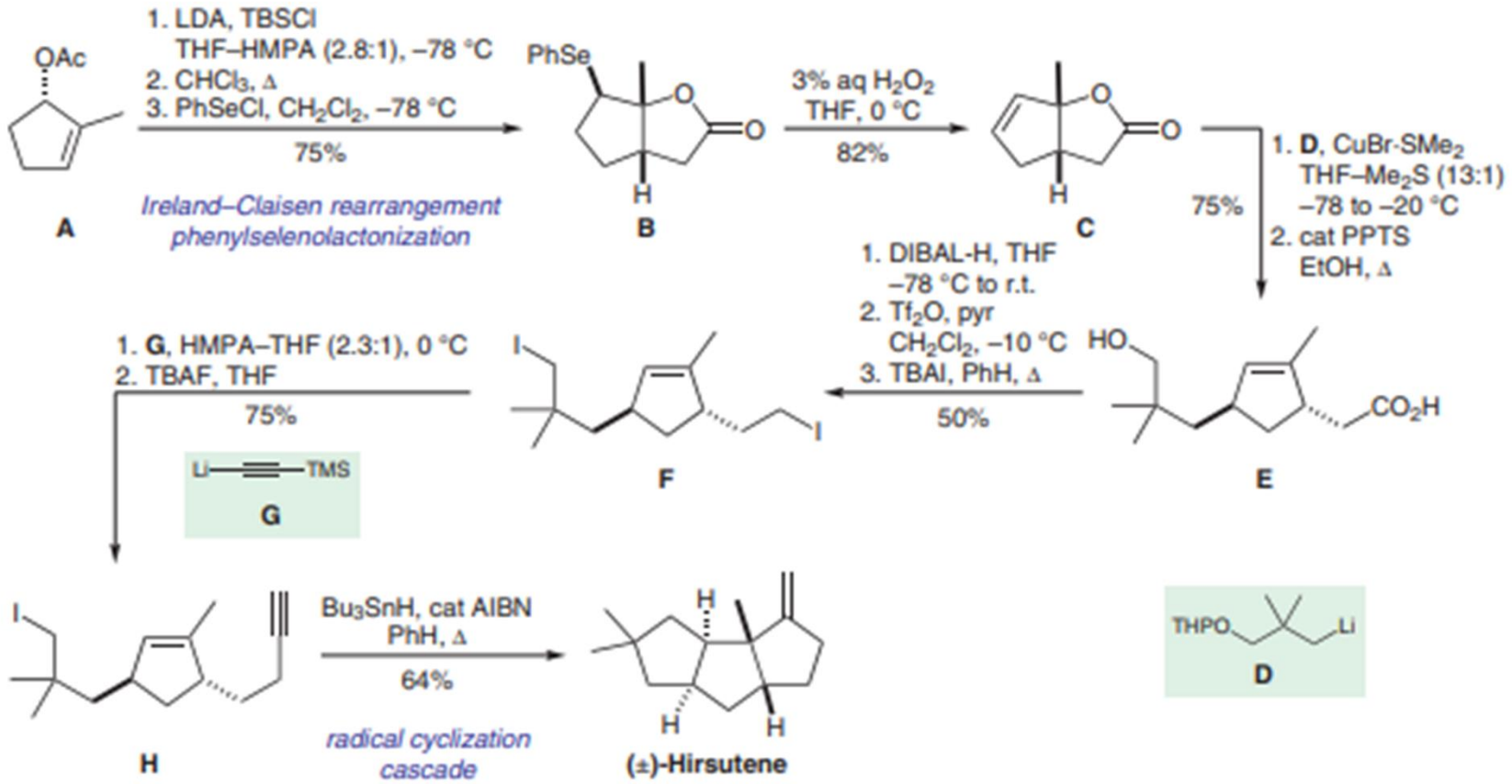
Curra'n Synthesis of Hirsutene (Kharasch addition reactions)

Hirsutene is a linear triquinane that was isolated from the fungi Coriolus consors. Lack of heteroatomic functional groups along with the presence of four contiguous stereocenters. Two quaternary carbon atoms render this condensed cyclopentanoid natural product.



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Steroids-An Introduction

A steroid is a biologically active organic compound with four rings arranged in a specific molecular configuration.

Steroids have two principal biological functions: as important components of cell membranes which alter membrane fluidity; and as signaling molecules.

Hundreds of steroids are found in plants, animals and fungi.

All steroids are manufactured in cells from the sterols lanosterol (opisthokonts) or cycloartenol (plants).

Lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene.

The steroid core structure is typically composed of seventeen carbon atoms, bonded in four "fused" rings: three six-member cyclohexane rings (rings A, B and C in the first illustration) and one five-member cyclopentane ring (the D ring).

Steroids vary by the functional groups attached to this four-ring core and by the oxidation state of the rings.

Sterols are forms of steroids with a hydroxy group at position three and a skeleton derived from cholestane.

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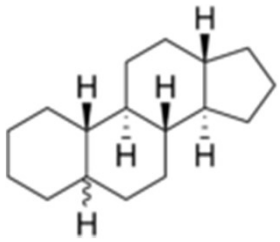
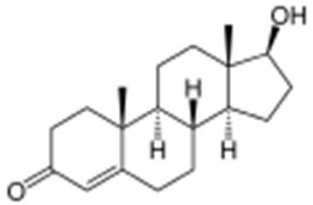
Steroids can also be more radically modified, such as by changes to the ring structure, for example, cutting one of the rings.

Cutting Ring B produces secosteroids one of which is vitamin D_3.

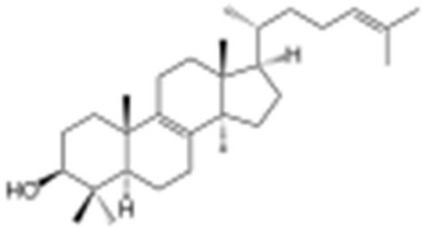
Examples include the lipid cholesterol, the sex hormones estradiol and testosterone, and the anti-inflammatory drug dexamethasone.



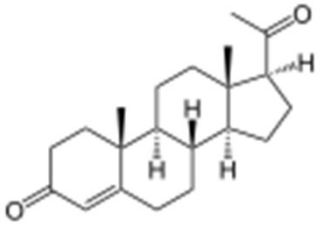
Gonane



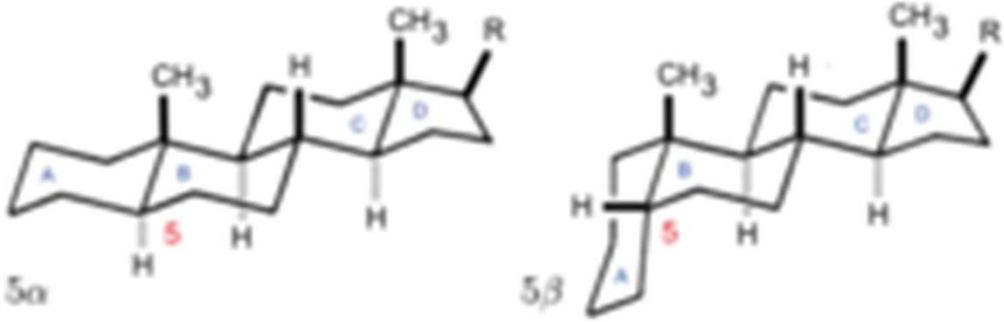
Testosterone



Lanosterol



Progesterone



Steroid 5α and 5β (stereoisomers)

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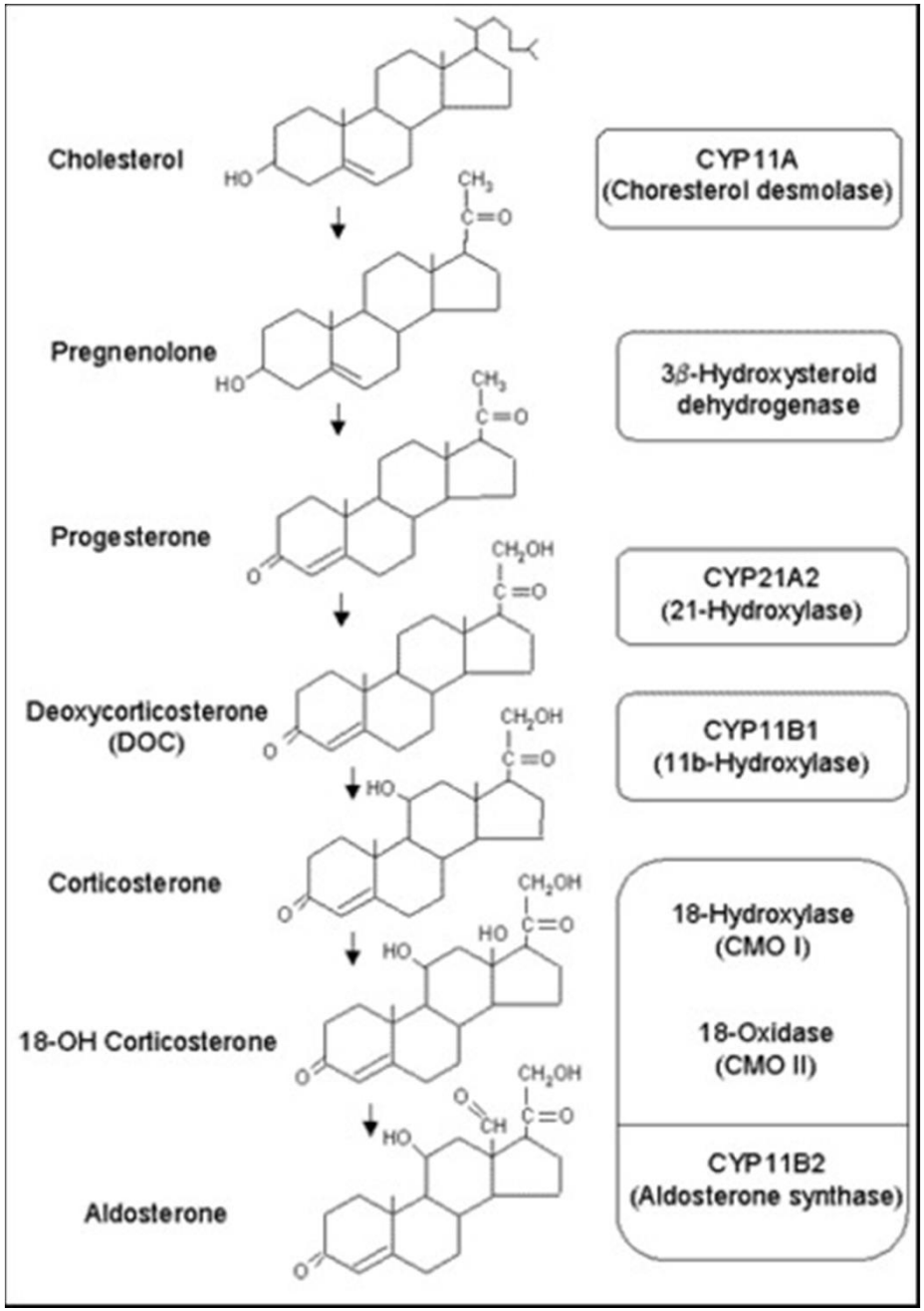
Aldosterone

Aldosterone is crucial for sodium conservation in the kidney, salivary glands, sweat glands and colon.

Aldosterone is synthesized exclusively in the zona glomerulosa of the adrenal gland.

Aldosterone promotes active sodium transport and excretion of potassium via the mineralocorticoid receptor (MR) and the resultant activation of specific amiloride-sensitive sodium channels (ENaC) and the Na-K ATP ase pump in the target tissues.

Destruction or dysfunction of the adrenal gland in conditions such as primary adrenal insufficiency, congenital adrenal hypoplasia, isolated mineralocorticoid deficiency, acquired secondary aldosterone deficiency (hyporeninemic hypoaldosteronism), acquired primary aldosterone deficiency and inherited enzymatic defects in aldosterone biosynthesis cause clinical symptoms and laboratory characteristics owing to aldosterone deficiency.



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Testosterone

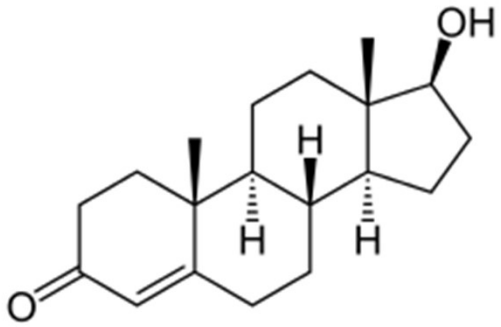
Testosterone is the primary sex hormone and anabolic steroid in males.

In male humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate.

Promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair.

In addition, testosterone is involved in health and well-being and the prevention of osteoporosis.

Insufficient levels of testosterone in men may lead to abnormalities including frailty and bone loss.



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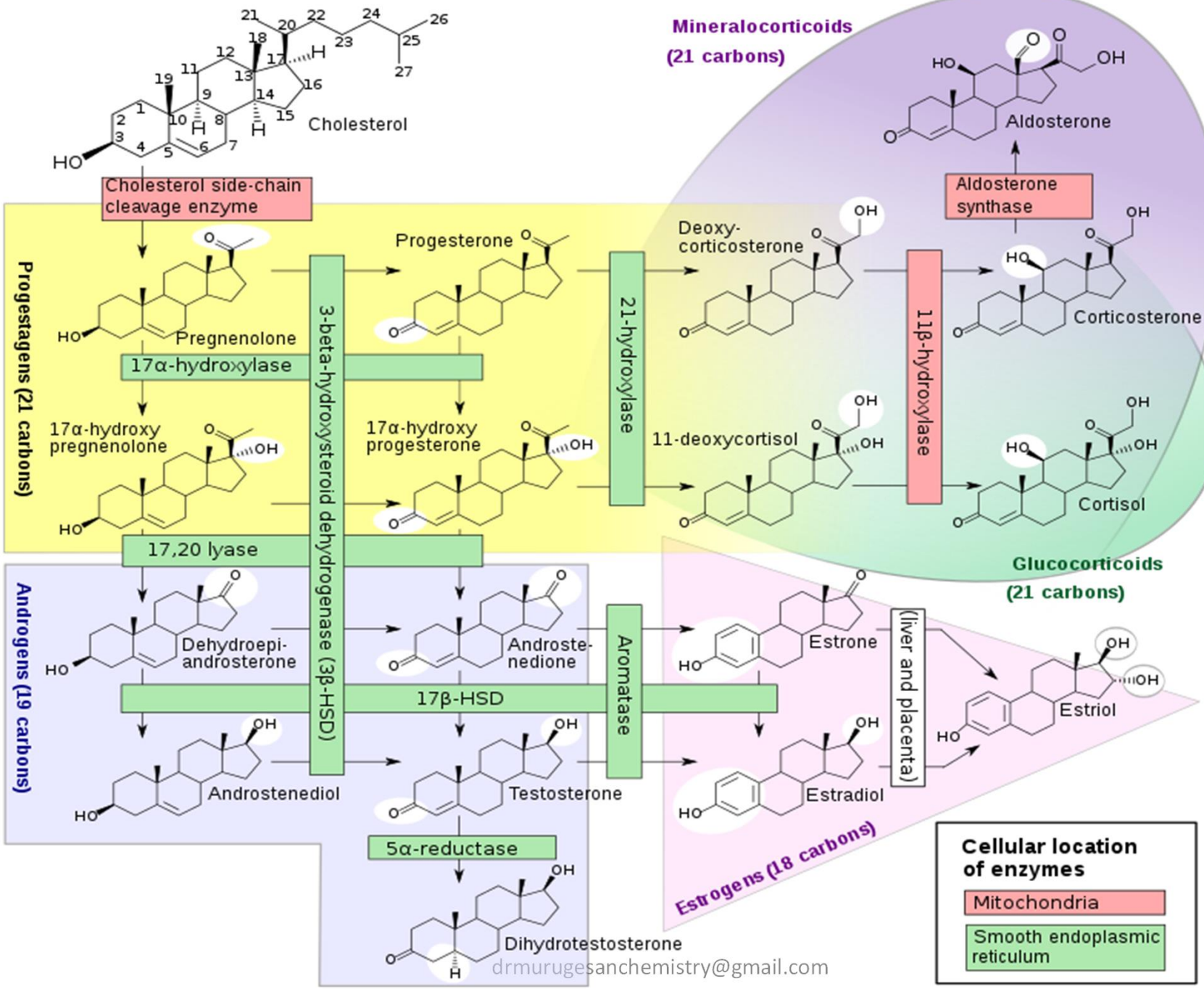


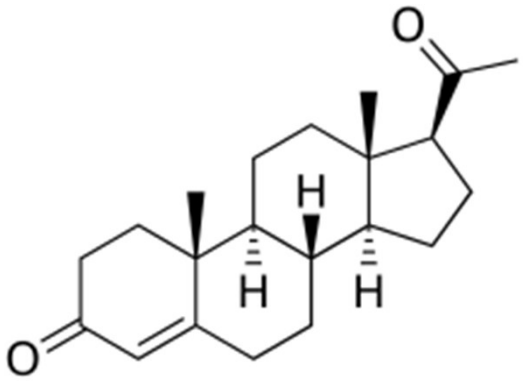
Progesterone

Progesterone is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species.

It belongs to a group of steroid hormones called the progestogens and is the major progestogen in the body.

Progesterone has a variety of important functions in the body. It is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids.

It plays an important role in brain function as a neurosteroid.



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The synthesis begins with reacting the phosphonium salt **7** with phenyl lithium to produce the phosphonium ylide **8**.

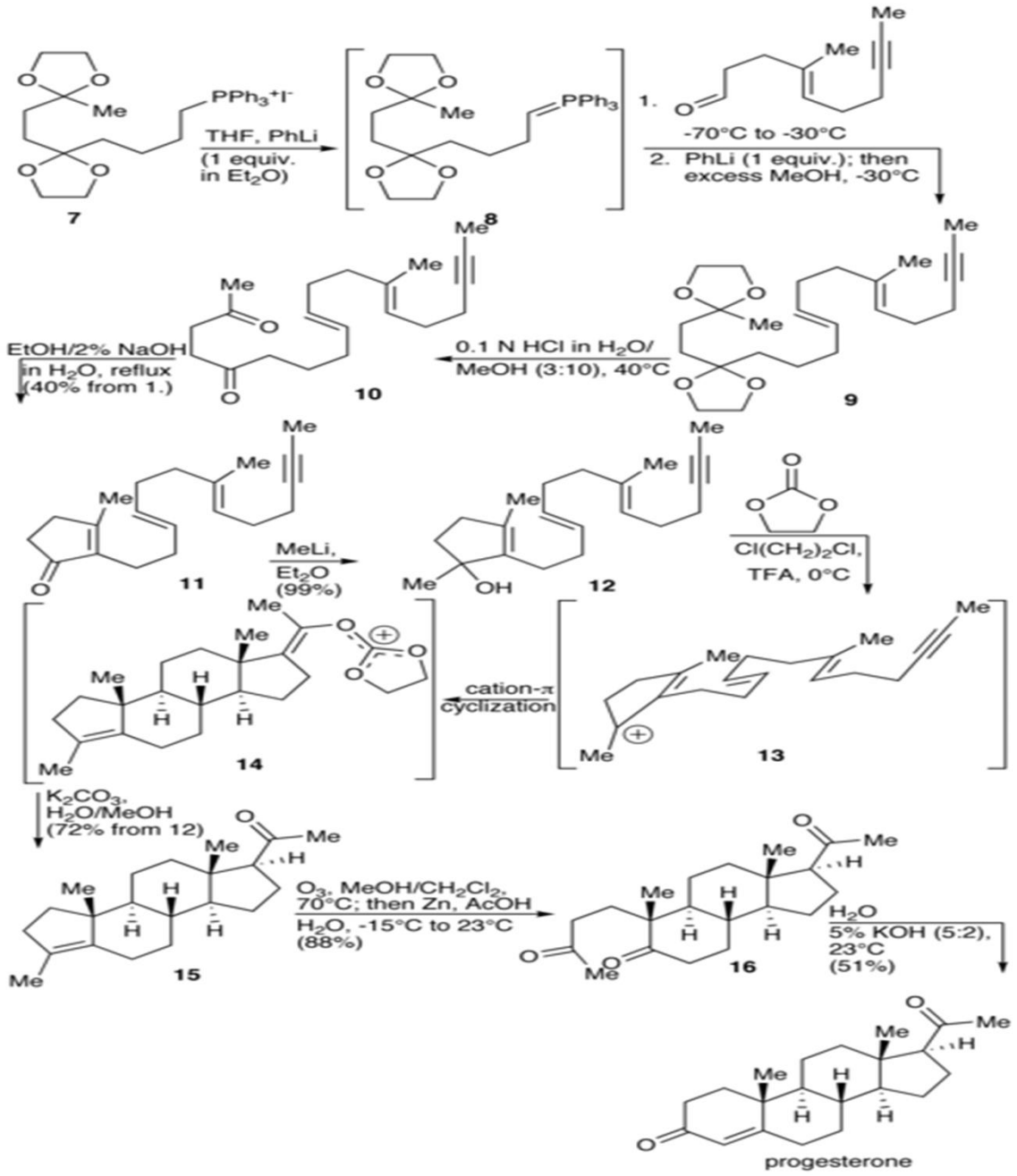
The ylide **8** is reacted with an aldehyde to produce the alkene **9**. The ketal protecting groups of **9** are hydrolyzed to produce the diketone **10**, which in turn is cyclized to form the cyclopentenone **11**.

The ketone of **11** is reacted with methyl lithium to yield the tertiary alcohol **12**, which in turn is treated with acid to produce the tertiary cation **13**. T

he key step of the synthesis is the π-cation cyclization of **13** in which the B-, C-, and D-rings of the steroid are simultaneously formed to produce **14**.

This step resembles the cationic cyclization reaction used in the biosynthesis of steroids and hence is referred to as *biomimetic*. In the next step the enol orthoester is hydrolyzed to produce the ketone **15**.

The cyclopentene A-ring is then opened by oxidizing with ozone to produce **16**. Finally, the diketone **17** undergoes an intramolecular aldol condensation by treating with aqueous potassium hydroxide to produce progesterone.



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Estrone

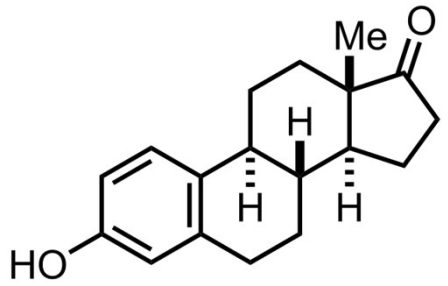
Estrone also spelled **oestrone**, is a steroid, a weak estrogen, and a minor female sex hormone.

It is one of three major endogenous estrogens, the others being estradiol and estriol.

Estrone, as well as the other estrogens, are synthesized from cholesterol and secreted mainly from the gonads, though they can also be formed from adrenal androgens in adipose tissue.

Relative to estradiol, both estrone and estriol have far weaker activity as estrogens.

Estrone can be converted into estradiol, and serves mainly as a precursor or metabolic intermediate of estradiol. It is both a precursor and metabolite of estradiol.



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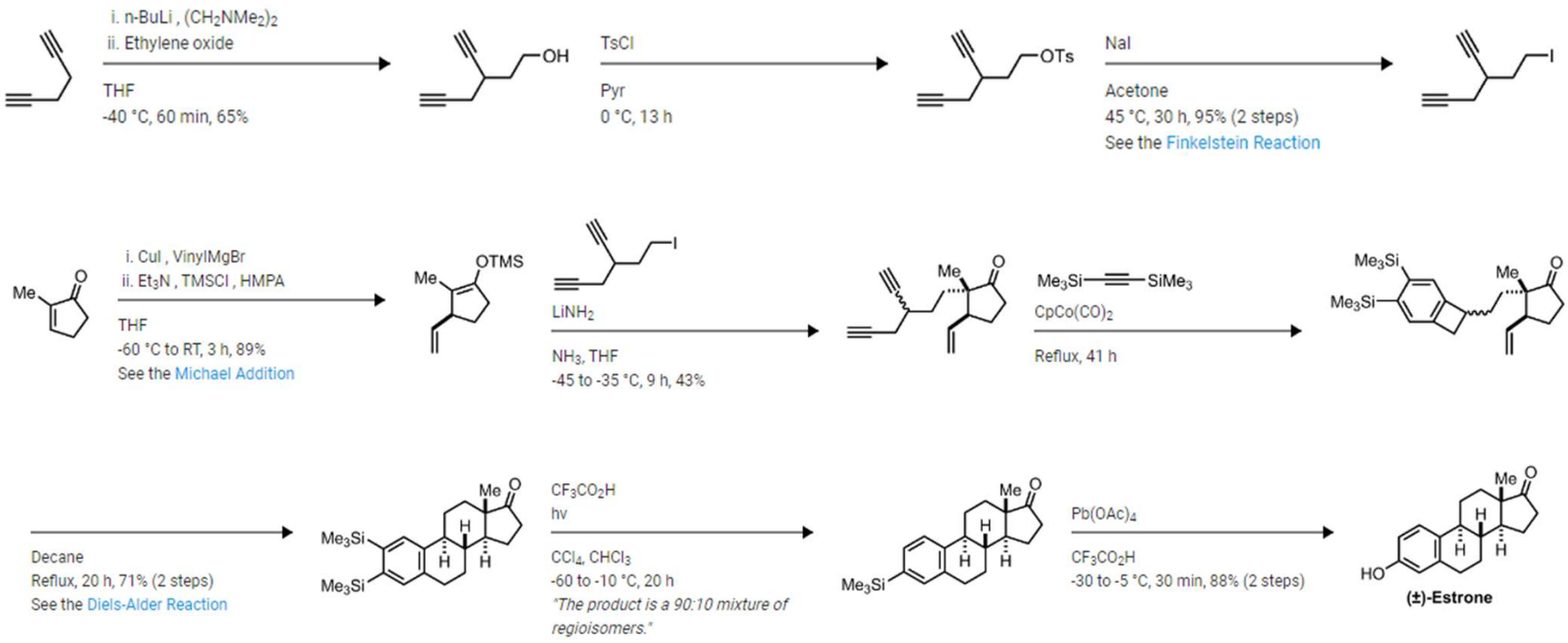

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Alkaloids

Alkaloids are a class of basic, naturally occurring organic compounds that contain at least one nitrogen atom. They are neutral and even weakly acidic properties.

Some synthetic compounds of similar structure may also be termed alkaloids.

In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus.

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals.

They can be purified from crude extracts by acid-base extraction, or solvent extractions followed by silica-gel column chromatography.

Alkaloids can be toxic too (*e.g.* atropine, tubocurarine).

Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly a bitter taste.

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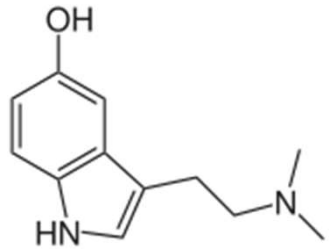
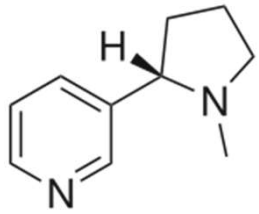
Alkaloids have a wide range of pharmacological activities including antimalarial (*e.g.* quinine), antiasthma (*e.g.* ephedrine), anticancer (*e.g.* homoharringtonine), cholinomimetic (*e.g.* galantamine), vasodilatory (*e.g.* vincamine), antiarrhythmic (*e.g.* quinidine), analgesic (*e.g.* morphine), antibacterial (*e.g.* chelerythrine), and antihyperglycemic activities (*e.g.* piperine).

Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (*e.g.* psilocin) and stimulant activities (*e.g.* cocaine, caffeine, nicotine, theobromine).

Alkaloids are often divided into the following major groups
True alkaloids
Protoalkaloids
Polyamine alkaloids
Peptide and cyclopeptide alkaloids
Pseudoalkaloids



Bufotenin



Nicotine

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Nicotine

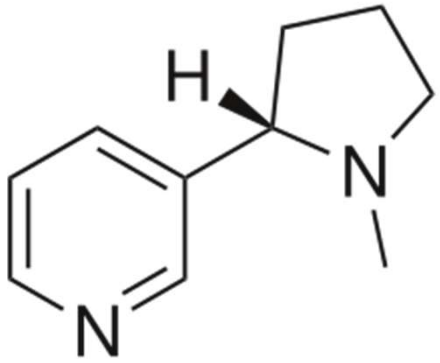
Nicotine is a widely used stimulant and potent parasympathomimetic alkaloid that is naturally produced in the nightshade family of plants.

It is used for smoking to relieve withdrawal symptoms.

Nicotine acts as a receptor agonist at most nicotinic acetylcholine receptors except at two nicotinic receptor subunits where it acts as a receptor antagonist.

Nicotine constitutes approximately 0.6–3 % of the dry weight of tobacco.

Nicotine is also present at concentrations of millionths of a percent in the edible family Solanaceae, including potatoes and tomatoes.



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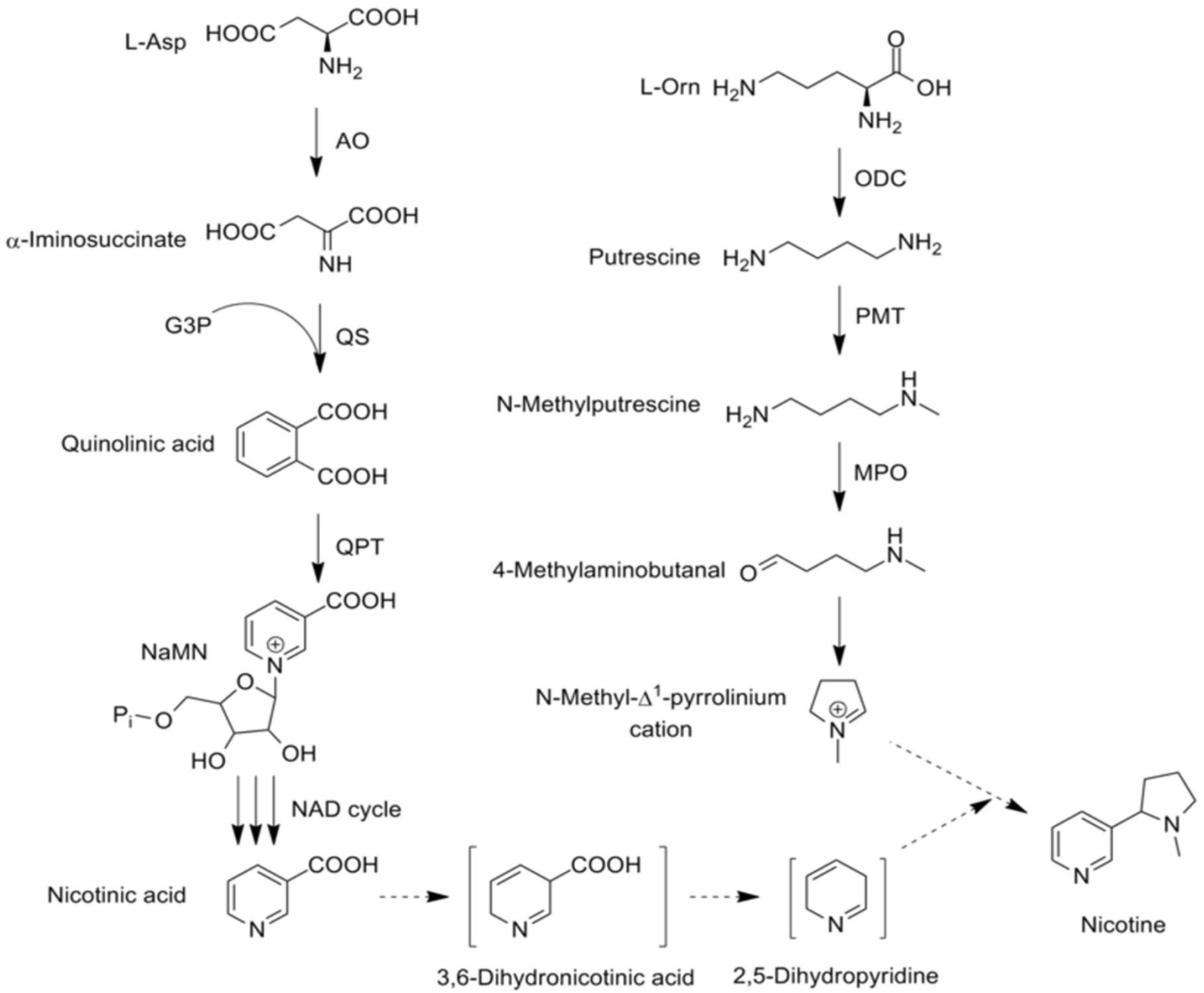

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Camptothecin (CPT)

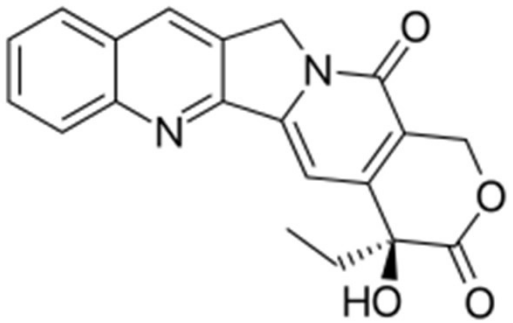
Camptothecin is a topoisomerase poison. A natural products for anticancer drugs.

It is isolated from the bark and stem of *Camptotheca acuminata* a tree native to China used as a cancer treatment in Traditional Chinese Medicine.

CPT showed remarkable anticancer activity in preliminary clinical trials. However, it has low solubility, so synthetic and medicinal chemists have developed numerous syntheses of camptothecin.

Four CPT analogues have been approved and are used in cancer chemotherapy.

Today, topotecan, irinotecan, belotecan, and trastuzumab deruxtecan.



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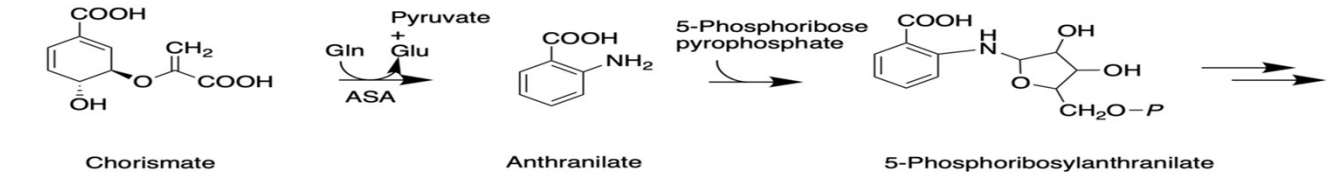
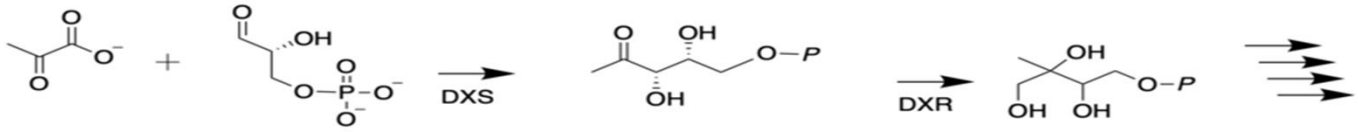
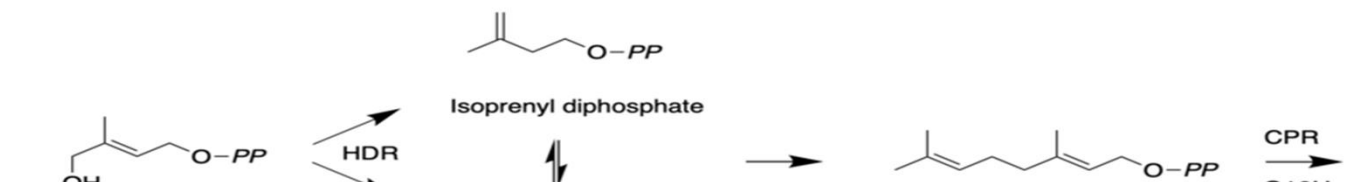


Chorismate Anthranilate 5-Phosphoribosylanthranilate

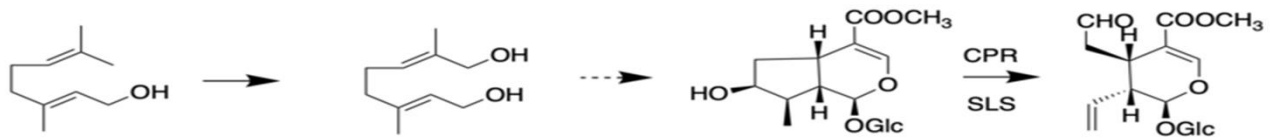
Indole glycerol phosphate Indole Tryptophan Tryptamine



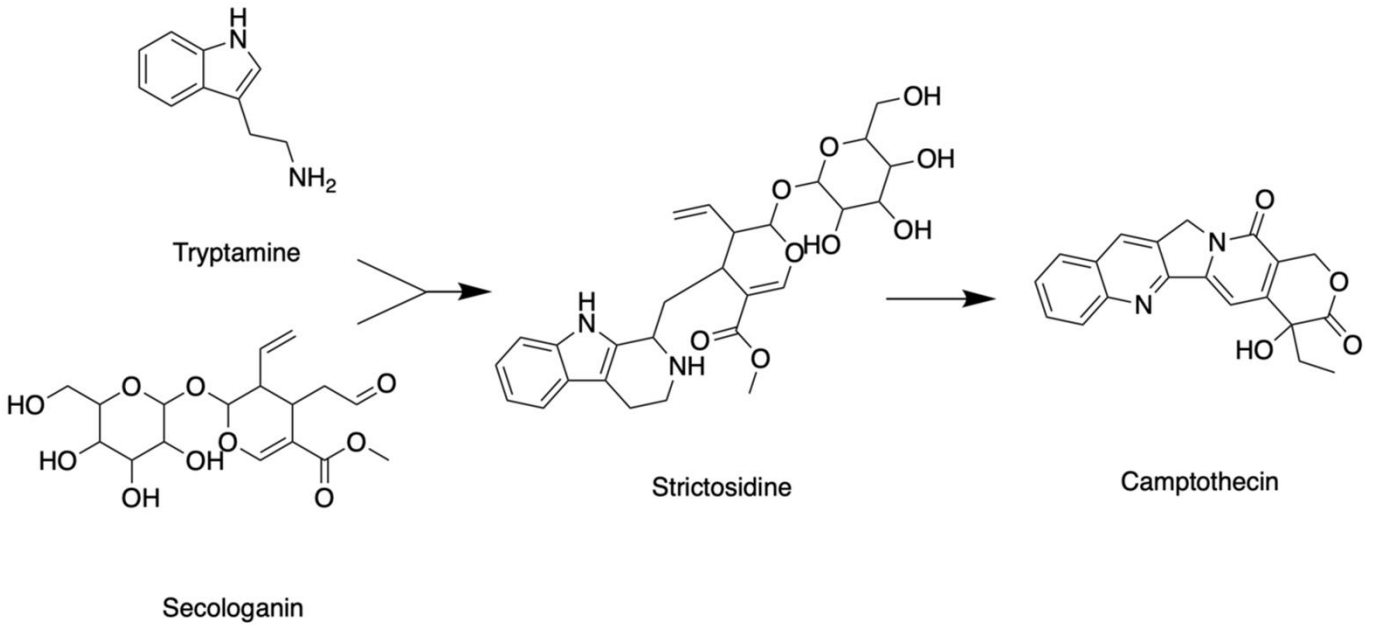
Pyruvate D-Glyceraldehyde-3-phosphate 1-Deoxy-D-xyluose-5-phosphate 2C-methyl-D-erythritol-4-phosphate



1-Hydroxy-2-methyl-2(*E*)-butenyl 4-diphosphate Geranyl diphosphate



Geraniol 10-Hydroxygeraniol Loganin Secologanin


Tryptamine
Secologanin
Strictosidine
Camptothecin

Epibatidine

A chlorinated alkaloid.

Epibatidine is toxic. Its toxicity stems from its ability to interact with nicotinic and muscarinic acetylcholine receptors.

With doses over 5 µg/kg, symptoms included hypertension (increased blood pressure), paralysis in the respiratory system and ultimately, death.

Studies show it has a potency at least 200 times that of morphine.

The Corey Synthesis of Epibatidine

The route consists of a 9 step synthesis, progressing via intermediates **2** to **10**.

The yields for individual steps are very high, and so overall the yield is just over 40%.

The *levo* and *dextro* forms of epibatidine can be easily separated by liquid chromatography.

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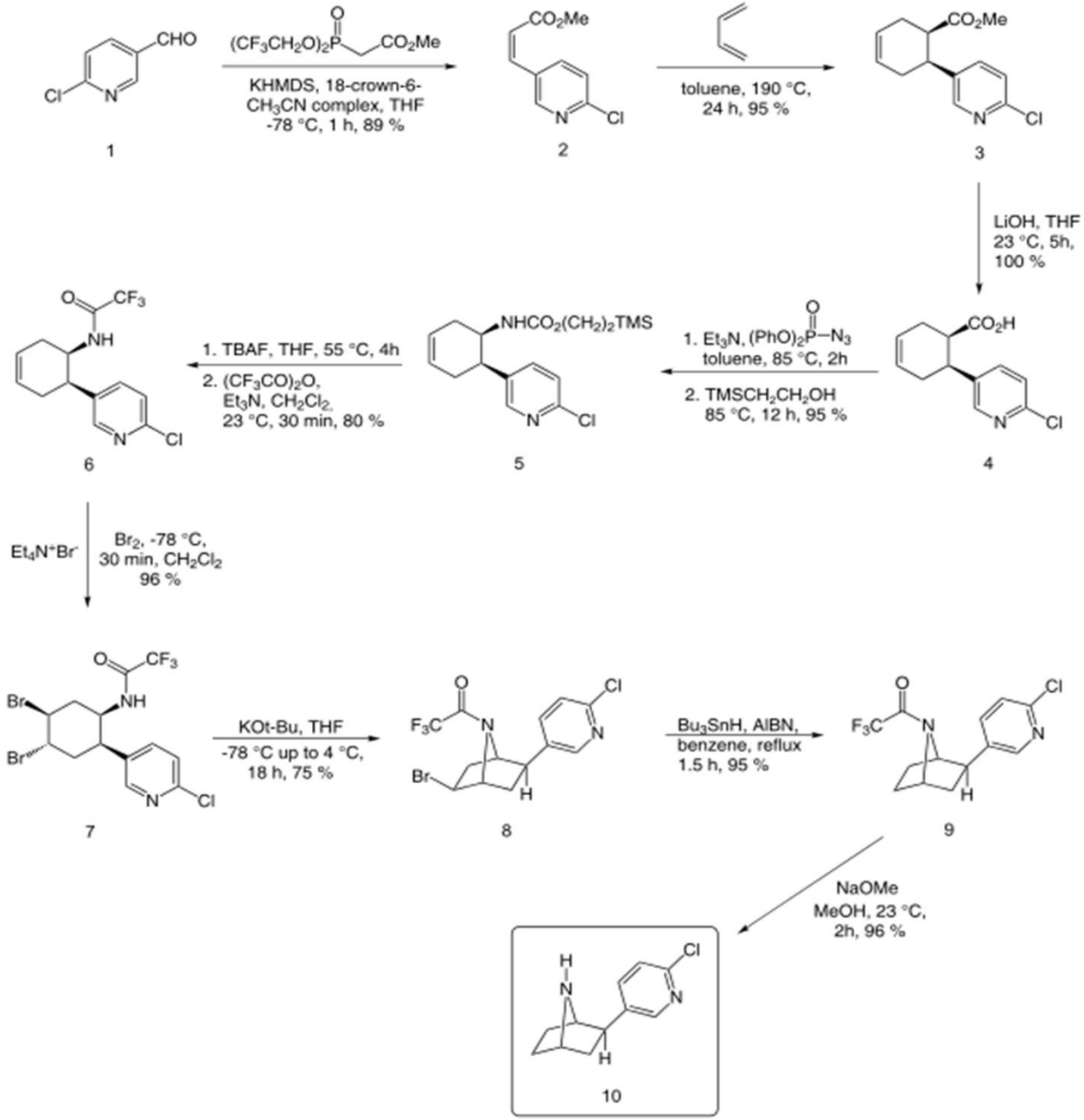

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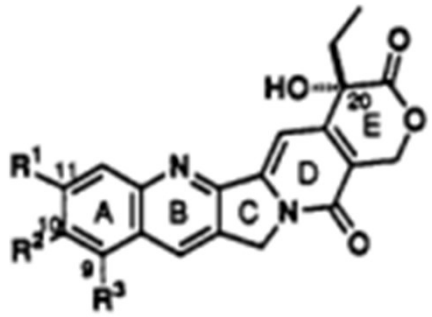
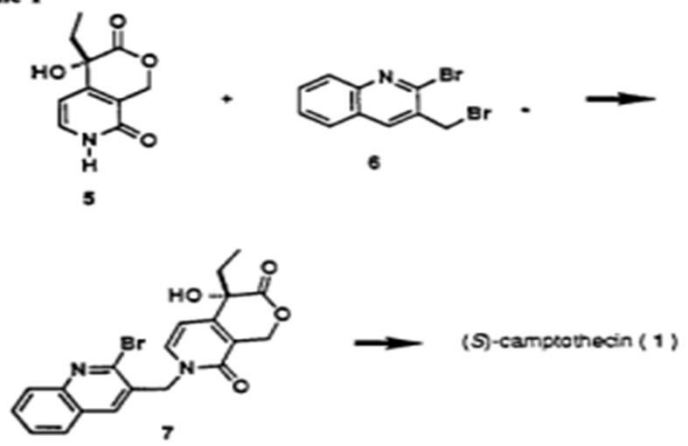
Comin's Asymmetric Synthesis of Camptothecin

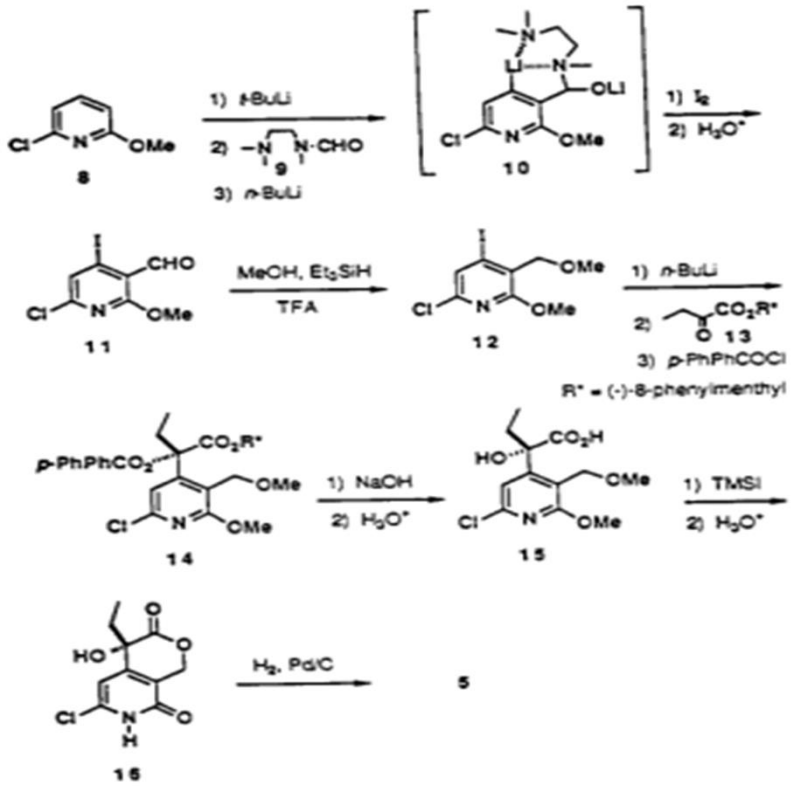
(*S*)-Camptothecin (**1**), a pentacyclic alkaloid isolated from *Camptotheca acuminata* by Wall and co-workers in 1966, continues to be one of the most important lead compounds among the anticancer natural products.[1] A number of promising analogs have been prepared that show improved solubility, low overall toxicity, and impressive in vivo activity against certain solid tumors.[2] Some of the more active derivatives include 9-aminocamptothecin[2a] (**2**), 10,11-(methylenedioxy)camptothecin[2a,3] (**3**), and (20*S*)-9-[(dimethylamino)methyl]-10-hydroxycamptothecin[2b] (**4**). Analog **4** is currently undergoing phase I clinical trials in cancer patients. The camptothecins' mode of action has been demonstrated to involve inhibition of DNA relaxation through interference with topoisomerase I function.[4] This novel activity and a recent report of potent anti-retroviral activity[5] for (*S*)-camptothecin have reenergized interest in this family of alkaloids.



Scheme I



Scheme II



Woodward's Synthesis of Reserpine

Reserpine is a drug that is used for the treatment of high blood pressure, usually in combination with a thiazide diuretic or vasodilator.

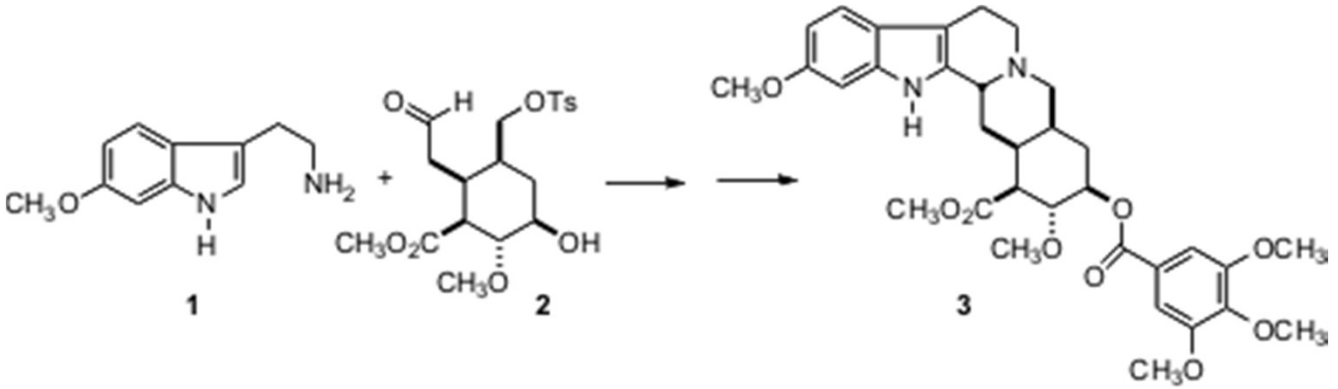
Large clinical trials have shown that combined treatment with reserpine plus a thiazide diuretic reduces mortality of people with hypertension.

These substances are normally involved in controlling heart rate, force of cardiac contraction and peripheral vascular resistance.

At doses of 0.05 to 0.2 mg per day, reserpine is well tolerated. The most common adverse effect being nasal stuffiness.

Reserpine has also been used for relief of psychotic symptoms.

Condensation of **2** with 6-methoxytryptamine (**1**) led to reserpine (**3**).



The preparation of **2** started with the enantioselective addition of acrylate to butadiene to give the acid **6**.

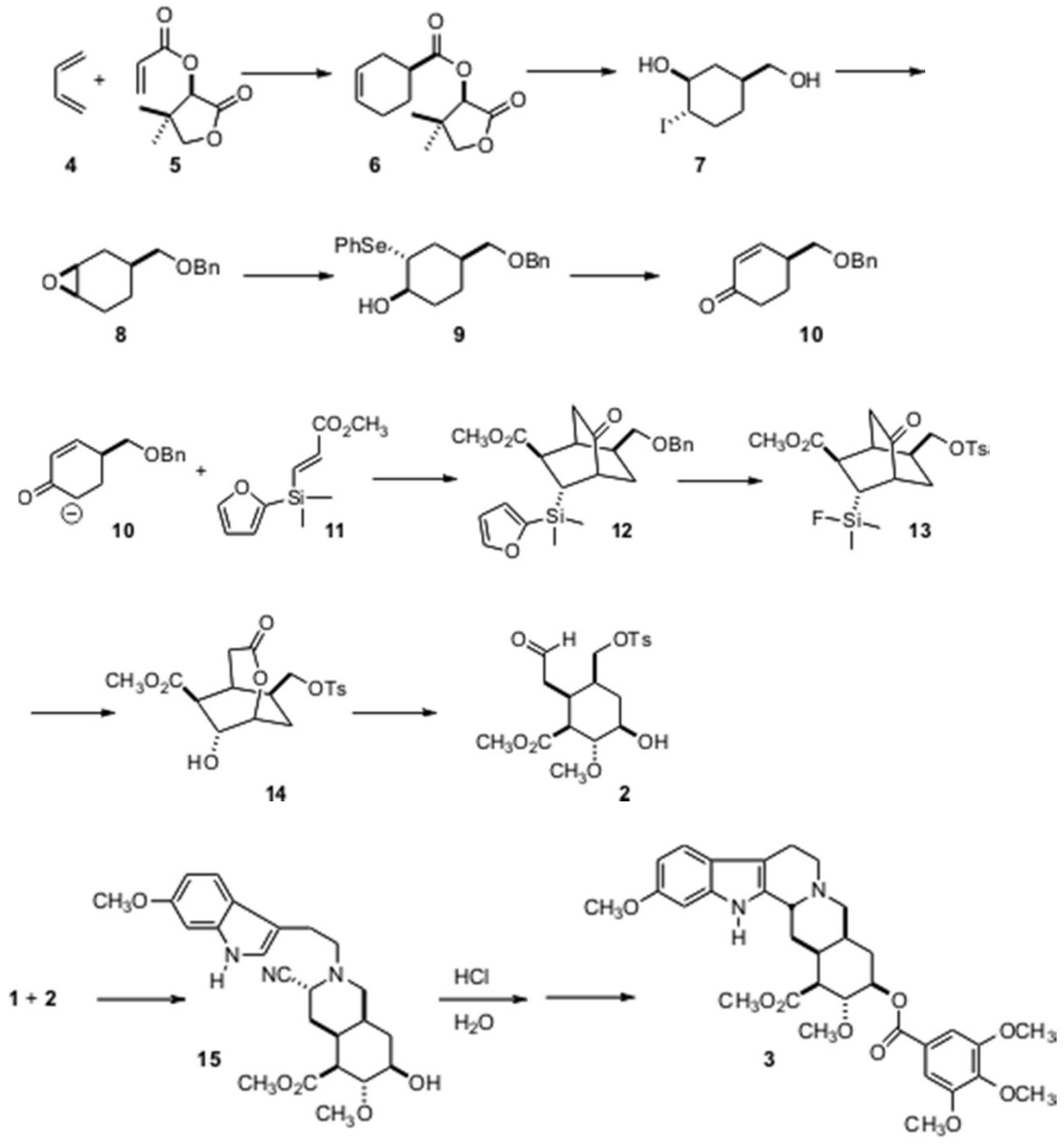
Iodolactone formation followed by reduction gave the diol **7**. Under the conditions of benzyl ether formation, the iodohydrin cyclized to the epoxide, giving **8**.

Phenyl selenide added to **8** to give the expected diaxial product **9**, which on oxidation gave **10** in high enantiomeric excess.

The addition of the kinetic lithium enolate of **10** to the silyl acrylate **11** to give **12**.

Which is debenzylated to the tosylate **13**. On exposure to two equivalents of hydrogen peroxide, the ketone underwent Baeyer-Villiger oxidation with high regioselectivity.

The silane was also oxidized, delivering **14**. On stirring at room temperature in aqueous HCl **15** did cyclize to the correct diastereomer, providing, after acylation, reserpine (**3**).



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